producing a pharmaceutical composition **comprising mixing a compound of claim 1 with a pharmaceutically acceptable carrier, diluent or bulking agent**.

REMARKS

I. Amendments

Claims 1, 12 and 21 have been amended, claims 29-35 have been added and claims 2, 3, 5, 6, 8, 15, 16, 18-20 and 22-24 have been canceled.

Typographical and grammatical errors have also been corrected throughout the specification.

This amendment adds no new matter to the specification. Support for this amendment is found in the specification and claims as filed.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "Version with Markings to Show Changes Made".

No change of inventorship is necessitated by this amendment.

II. Discussion of the Restriction Requirement

Claims 1-28 have been subjected to a restriction requirement. By this amendment, Applicants confirm the election of Group I, drawn to cephalosporins (Y= S), claims 5 and 12.

By this amendment, Applicants have amended claim 1 to conform with the restriction requirement, and cancelled claim 5. Therefore, Applicants submit that the claims as amended conform with the imposed restriction requirement.

III. Discussion of the Rejection for Improper Markush Grouping

Claims 1-4, 6-11 and 13-28 have been rejected under a judicially-created doctrine as being drawn to an improper Markush grouping.

By this amendment, Applicants have amended claim 1 to conform with the restriction requirement, and cancelled claim 5. Claims 2, 3, 6, 8, 15, 16, 18-20 and 22-24 have also been cancelled. Claims 4, 7, 9-11, 13, 14, 17, 21 and 25-28 depend upon claim 1. Applicants

submit that the present amendment of claim 1 renders all of the claims drawn to a proper Markush grouping. Therefore, Applicants respectfully request withdrawal of the rejection for improper Markush grouping.

IV. **Discussion of the Rejection under 35 U.S.C. Sec. 112, Second Paragraph**

Claims 1-11 and 14-28 have been rejected under 35 U.S.C. Sec. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Office Action stated that: 1) the scope of "a group convertible to a phosphono group" in claim 1 is unclear; 2) the term "protected" in claim 2 is unclear; 3) the phrase "group having a linkage through a carbon atom" in claim 1 is unclear; 4) the term "substituted" in the claims is unclear; 5) the term "heterocyclic" in the claims is indefinite; 6) claim 15 contains functional language, and does not appear to give the zwitterion set forth in claim 1; 7) claim 16 does not recite a carrier; 8) claims 18 and 19 fail to further limit claim 16; 9) claims 21-24 are incomplete; and 10) the term "quaternized" in claim 1 is vague. A discussion of each aspect of the rejection follows.

Concerning the first aspect of the rejection, by this amendment, Applicants have modified the definition of R^1 by removing "a group convertible to a phosphono group" and adding the definition of R^1 from claim 3 to claim 1.

Concerning the second aspect of the rejection, by this amendment, Applicants have cancelled claim 2, rendering the rejection as to this claim moot.

Concerning the third aspect of the rejection, by this amendment, Applicants have modified the definition of R^2 in claim 1 by removing the phrase "group having a linkage through a carbon atom" and adding the definition of R^2 from claim 6 to claim 1.

Concerning the fourth aspect of the rejection, the Examiner believes that the term "substituted" in the claims is unclear. Applicants submit that the specification sufficiently defines substituents of R^2 at page 8, line 5- page 11, line 24; and substituents of R^3 and R^4 at page 13, lines 13-16 *inter alia*.

Concerning the fifth aspect of the rejection, the Examiner believes that the term "heterocyclic" is unclear. Applicants submit that the heterocyclic group formed by linkage of R^3 and R^4 is sufficiently defined on page 13, lines 6-16 of the specification.

Concerning the sixth aspect of the rejection, Applicants have cancelled claim 15 by this amendment, rendering the rejection as to this claim moot.

Concerning the seventh aspect of the rejection, Applicants have cancelled claim 16 by this amendment, rendering the rejection as to this claim moot.

Concerning the eighth aspect of the rejection, Applicants have cancelled claims 18 and 19 by this amendment, rendering the rejection as to these claims moot.

Concerning the ninth aspect of the rejection, Applicants have cancelled claims 21-24 by this amendment, rendering the rejection as to these claims moot.

Concerning the tenth aspect of the rejection, the Examiner believes that the term "quaternized" in the claims is unclear. By this amendment, Applicants have modified claim 1 to include the quaternized nitrogen-containing heterocyclic ring as defined in claim 8.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 1-11 and 14-28 under 35 U.S.C. Sec. 112, second paragraph.

V. Discussion of the Rejection under 35 U.S.C. Sec. 102(b)

Claims 1, 5-11 and 13-28 have been rejected under 35 U.S.C. Sec. 102 (b) as being unpatentable over JP 9-100283. Specifically, the Office Action stated that the reference compounds disclose similar compounds, with the exception that R^1 is a protected amino group for the cited reference, whereas R^1 is a phosphono group or a group convertible to a phosphono group in the present specification.

By this amendment, Applicants have limited R^1 to the specific substituents originally disclosed in claim 3. Applicants submit that the present invention, as set forth in claim 1 as amended, is not anticipated by the cited reference.

Moreover, Applicants have attached a copy of the translation of the cited reference as Appendix A, for the Examiner's review. Applicants wish to point out that R^1 in the cited reference represents an amino group which may be protected, wherein suitable protecting groups are disclosed on page 7, paragraph 7 of the translation. The phosphono derivatives set forth in claim 1 as amended are not among the protecting groups disclosed by the cited reference. Moreover, Applicants also note that in Examples 1-46 of the cited reference, no protected amino groups were synthesized at all. In the Examples, R^1 is only $-NH_2$, as illustrated in the Tables on pages 42-47 of the translation. Therefore, Applicants do not believe that the cited reference anticipates their invention as set forth in claim 1 as amended.

Claims 7, 9-11, 13, 14, 17, 21 and 25-28 depend upon claim 1, so Applicants submit that the more specific dependent claims are also not anticipated by the cited reference, and as claims

5, 6, 8, 15, 16, 18-20 and 22-24 have been cancelled, Applicants respectfully request withdrawal of the Sec. 102 (b) rejection.

VI. Discussion of the Rejection under 35 U.S.C. Sec. 103(a)

Claims 1-28 have been rejected under 35 U.S.C. Sec. 103 (a) as being unpatentable over JP 9-100283 in view of Teraji *et al.* (1986) or Teraji *et al.* (1981). Specifically the Office Action stated that since the cited references of Teraji *et al.* note the advantages arising from the use of phosphono derivatives, that one of ordinary skill in the art would have been motivated to obtain the same advantage by using the same derivatives of the compounds disclosed in JP 9-100283.

Applicants submit that their invention, as set forth in the claims as amended, is not obvious over the combination of the cited reference, as surprising and unexpected results are obtained for compounds representative of the present invention when compared to a compound of the cited JP 9-100283 reference.

By this amendment, Applicants submit a Declaration from Dr. Horibe which proves the superiority of a compound of the present invention (compound A in the Declaration, which is the compound of claim 12, and a representative compound of claim 1 in the present application) over a compound having $R^1 = NH_2$ (compound B), as taught by the cited reference JP 9-100283. As previously indicated, JP 9-100283 only discloses examples having $R^1 = NH_2$. The stability of the two compounds in water over a forty-eight hour period were compared, and the Declaration indicates that compound A was more stable than compound B, as 4% more of compound A remained than compound B at the end of the test period. Moreover, at twelve hours, 96.9% of compound A remained in the aqueous solution, while only 94.7% of compound B remained in aqueous solution.

This difference in stability is significant for the following reason. As many hospitals require that at least 95% of the compound remain 12 hours after dissolution for an injectable compound, compound B is unacceptable, whereas compound A is acceptable. In the Japanese reference, the table on pages 29-34 shows that no compounds synthesized had any R^1 except for NH_2. The Declaration thus shows a significant and unexpected difference between compounds of the cited Japanese reference and the compounds of the present invention.

As the difference in stability of the two comparative compounds is both significant and unexpected, and such result would not be obvious to one skilled in the art, Applicants do not believe that their invention, as set forth in the claims as amended, is taught or

suggested by the combination of the Japanese reference with the two Teraji *et al.* references. Therefore, Applicants respectfully request withdrawal of the Sec. 103(a) rejection.

New claims 29-35 have been added. Claims 29-34 depend upon claim 12. Applicants submit that these new claims are also non-obvious over the combination of the cited references.

VII. **Conclusion**

Reconsideration of the claims as amended and allowance is requested. Should the Examiner believe that a conference with Applicants' attorney would advance prosecution of this application, the Examiner is respectfully requested to call Applicants' attorney at (847) 383-3391.

Respectfully submitted,

Dated: October 9, 2001

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APPENDIX A

(19) Japanese Patent Office (JP)

(12) Unexamined Patent Publication (A)

(11) Patent Application Publication Number

Kokai No. 9-100283

(43) [Publication Date] April 15, 1997

(51) Int. Cl.[6]	Identification Number	Serial Number	FI		Column for Technical Indication
C07D 519/06			C07D 519/00	385	
A61K 31/545	ADZ		A61K 31/545	ADZ	
C07D 501/36	114	9164-4C	C07D 501/36	114	

Request for Examination: Not requested

Number of Claims: 13 OL (48 pages in total)

(21) Application Number : Tokugan 8-189327
(22) Filing Date : July 18, 1996
(31) Claim of Priority Number: Tokugan 7-182367
(32) Priority Date : July 19, 1995
(33) Claim of Priority Nation : Japan (JP)
(31) Claim of Priority Number: Tokugan 7-193686
(32) Priority Date : July 28, 1995
(33) Claim of Priority Nation : Japan (JP)

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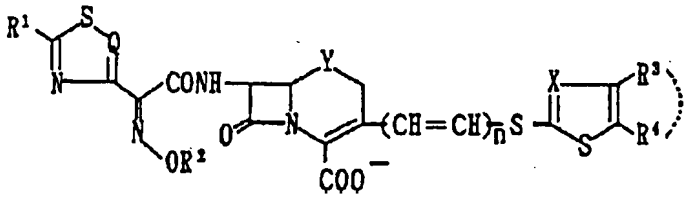
(54) [Title of the Invention] Cefem Compound, Method of Its Production, and Antibacterial Composition

(57) [Abstract of the Disclosure]

[Problem to be Solved] To provide an antibacterial agent possessing excellent antibacterial activity against gram-positive bacteria, including MRSA, and gram-negative bacteria.

[Means of Solving the Problem] A compound represented by the formula:

[Formula 1]

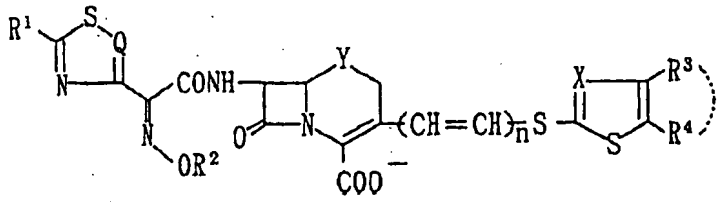


[wherein R^1 represents NH_2 which may be protected; R^2 represents H or a group bound via C; one of R^3 and R^4 represents a pyridinium group which may be substituted, the other representing H or a hydrocarbon group which may be substituted, or R^3 and R^4 may bind together to form a heterocyclic ring which contains quaternized N, and which may be substituted; each of Q and X represents N or CH; Y represents S, O or CH_2; n represents 0 or 1; when n is 0, Y represents S or O], or an ester thereof or a salt thereof, a method of its production, and a pharmaceutical composition.

[Scope of Claims]

[Claim 1] A compound represented by the formula:

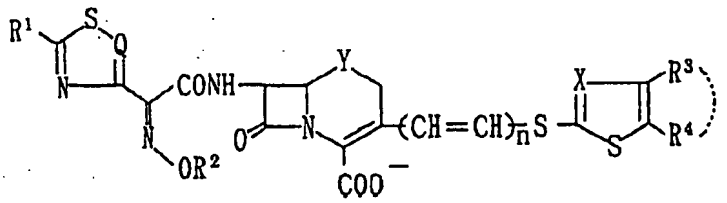
[Formula 1]



[wherein R^1 represents an amino group which may be protected; R^2 represents a hydrogen atom or a group bound via a carton atom; one of R^3 and R^4 represents a pyridinium group which may be substituted, the other representing a hydrogen atom or a hydrocarbon group which may be substituted, or R^3 and R^4 may bind together to form a heterocyclic ring which contains a quaternized nitrogen atom, and which may be substituted; each of Q and X represents a nitrogen atom or CH; Y represents S, O or CH_2; n represents 0 or 1; when n is 0, Y represents S or O], or an ester thereof or a salt thereof.

[Claim 2] A compound represented by the formula:

[Formula 2]



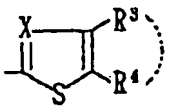
[wherein the symbols have the same definitions as those given in claim 1], or an ester thereof or a salt thereof.

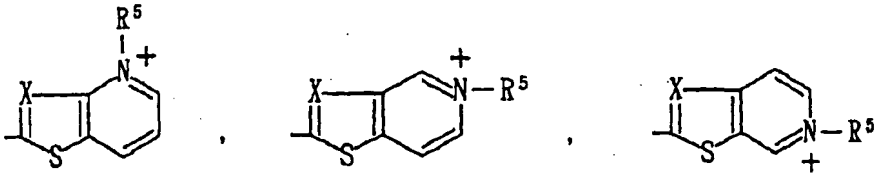
[Claim 3] A compound according to claim 1, wherein R^2 is a $C_{1\text{-}6}$ alkyl group which may be substituted or a $C_{3\text{-}5}$ cycloalkyl group.

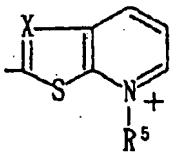
[Claim 4] A compound according to claim 1, wherein R^3 is a pyridinium group which may be substituted and R^4 is a hydrogen atom.

[Claim 5] A compound according to claim 1, wherein the group represented by:

[Formula 3]


is a group represented by:



or 

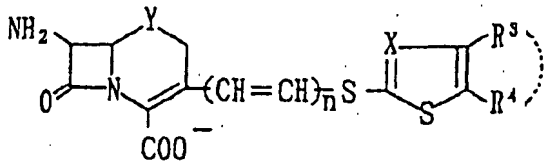
[wherein R^5 represents a hydrocarbon group which may be substituted].

[Claim 6] A compound according to claim 1, wherein Q is a nitrogen atom.

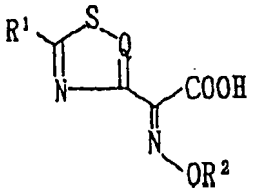
[Claim 7] A compound according to claim 1, wherein X is a nitrogen atom.

[Claim 8] A compound according to claim 1, wherein n is 1.

[Claim 9] A method of producing a compound according to claim 1, comprising reacting a compound represented by the formula:
[Formula 4]

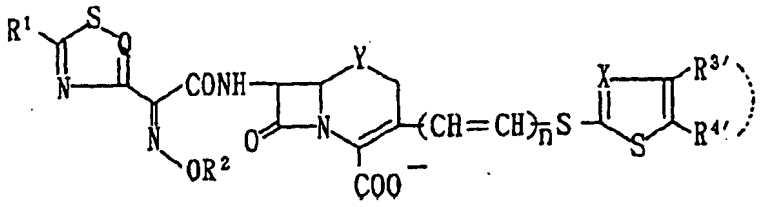


[wherein the symbols have the same definitions as tl given in claim 1], or an ester thereof or a salt thereof, and a carboxylic acid represented by the formula:
[Formula 5]



[wherein the symbols have the same definitions as those given in claim 1], or a salt thereof or a reactive derivative thereof, and, if necessary, removing a protective group.

[Claim 10] A method of producing a compound according to claim 1, comprising quaternizing a nitrogen atom in a pyridyl group which is represented by $R^{3'}$ or $R^{4'}$, and which may be substituted, or in a heterocyclic ring which contains a nitrogen atom, which may be substituted, and which is formed by $R^{3'}$ and $R^{4'}$ binding together, in a compound represented by the formula:
[Formula 6]



[wherein one of $R^{3'}$ and $R^{4'}$ represents a pyridyl group which may be substituted, the other representing a hydrogen atom or a hydrocarbon group which may be substituted, or $R^{3'}$ and $R^{4'}$ may bind together to form a heterocyclic ring which contains a nitrogen atom, and which may be substituted; the other symbols have the same definitions as those given in claim 1], or an ester thereof or a salt thereof, and, if necessary, removing a protective group.

[Claim 11] A pharmaceutical composition containing a compound according to claim 1.

[Claim 12] A pharmaceutical composition according to claim 11, which is an antibacterial composition.

[Claim 13] A pharmaceutical composition according to claim 11, which is an anti-MRSA agent.

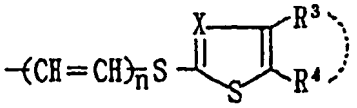
[Detailed Description of the Invention]
[0001]
[Field of the Invention]
The present invention relates to a new cefem compound which exhibits excellent antibacterial action on a broad spectrum of gram-positive bacteria and gram-negative bacteria, especially staphylococci and methicillin-resistant *Staphylococcus aureus* (MRSA), a method of its production, and an antibacterial composition.

[0002]
[Prior Art]
A cefem compound having a 2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-oximinoacetamide group at the 7-position and a thiazolylthio group at the 3-position is disclosed in Japanese Unexamined Patent Publication kokai No. 5-255345, and a cefem compound having a 2-(2-aminothiazol-4-yl)-2(Z)-oximinoacetamide group at the 7-position and a thiazolylthio group at the 3-position is disclosed in Japanese Unexamined Patent Publication kokai No. 4-321691. However, these publications do not describe that a pyridiniumthiazolylthio or thiazolopyridiniumthio group may be present as a substituent at the 3-position.

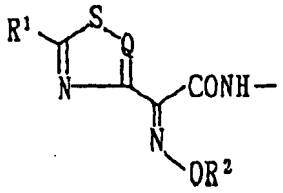
[0003]
[Problems to Be Solved by the Invention]
Conventional cefem compounds are unsatisfactory in terms of the spectrum and potency of antibacterial activity. Conventional cephalosporin compounds, in particular, are unsatisfactory in terms of antibacterial action against staphylococci, methicillin-resistant *Staphylococcus aureus* (MRSA), etc. MRSA, in

particular, has recently caused serious infectious diseases. There has been a demand for the advent of a new compound that has resolved this problem.

[0004]
[Means of Solving the Problems]
In view of the above circumstances, the present inventors conducted extensive investigations and for the first time succeeded in synthesizing a cefem, oxacefem or carbacefem compound which is structurally characterized by the presence of both a group represented by the formula:
[Formula 7]

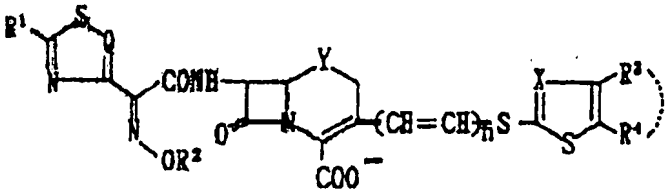


[wherein one of R^3 and R^4 represents a pyridinium group which may be substituted, the other representing a hydrogen atom or a hydrocarbon group which may be substituted, or R^3 and R^4 may bind together to form a heterocyclic ring which contains a quaternized nitrogen atom, and which may be substituted; X represents a nitrogen atom or CH; n represents 0 or 1] at the 3-position of the cefem, oxacefem or carbacefem backbone, and a group represented by the formula:
[Formula 8]



[wherein R^1 represents an amino group which may be substituted; R^2 represents a hydrogen atom or a group bound via a carbon atom; Q represents a nitrogen atom or CH] at the 7-position, or an ester thereof or a salt thereof. Furthermore, the present inventors found that the thus-synthesized compounds, based on the aforementioned unique chemical structure, unexpectedly exhibit a broad spectrum of excellent antibacterial action against gram-positive bacteria, including staphylococci and MRSA, and gram-negative bacteria etc. The inventors conducted further investigations based on these findings and developed the present invention.

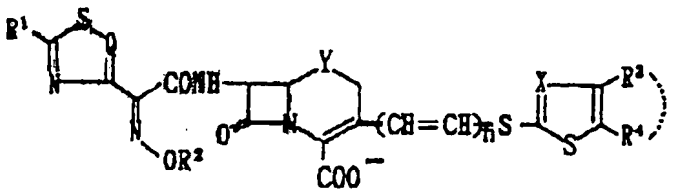
[0005] Accordingly, the present invention relates to: (1) a compound represented by formula [I]:
[Formula 9]



(I)

[wherein Y represents S, O or CH_2; the other symbols have the same definitions as those given above; when n is 0, Y represents S or O], or an ester thereof or a salt thereof, (2) a compound represented by formula [I']:

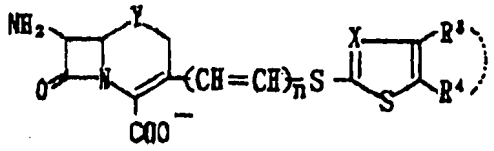
[Formula 10]



[I']

[wherein the symbols have the same definitions as those given above], or an ester thereof or a salt thereof, (3) a method of producing a compound according to (1) above, comprising reacting a compound represented by formula [II]:

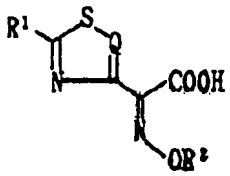
[Formula 11]



[II]

[wherein the symbols have the same definitions as those given above], or an ester thereof or a salt thereof, and a carboxylic acid represented by formula [III]:

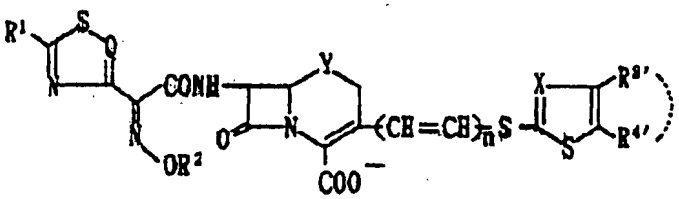
[Formula 12]



[III]

[wherein the symbols have the same definitions as those given above], or a salt thereof or a reactive derivative thereof, and, if necessary, removing a protective group, (4) method of producing a compound according to (1) above, comprising quaternizing a nitrogen atom in a pyridyl group which is represented by $R^{3'}$ or $R^{4'}$, and which may be substituted, or in a heterocyclic ring which contains a nitrogen atom, which may be substituted, and which is formed by $R^{3'}$ and $R^{4'}$ binding together, in a compound represented by formula [IV]:

[Formula 13]



[IV]

[wherein one of $R^{3'}$ and $R^{4'}$ represents a pyridyl group which may be substituted, the other representing a hydrogen atom or a hydrocarbon group which may be substituted, or $R^{3'}$ and $R^{4'}$ may bind together to form a heterocyclic ring which contains a nitrogen atom, and which may be substituted; the other symbols have the same definitions as those given in claim 1], or an ester thereof or a salt thereof, and, if necessary, removing a protective group, and (5) a pharmaceutical composition containing a compound according to

(1) above, etc.

[0006] The term "cefem compound" as used herein refers to a class of compounds designated on the basis of "cefam" described in "The Journal of the American Chemical Society," Vol. 84, p. 3400 (1962), meaning a cefam compound having a double bond at the 3,4-position. The compounds of the present invention include a compound of formula [I], which occurs in a free form, or an ester thereof or a salt thereof (salt of compound [I] or salt of ester of compound [I]). In the present specification, a compound of formula [I], which occurs in a free form, or an ester thereof or a salt thereof, is hereinafter simply abbreviated compound [I], antibacterial compound [I] or a compound represented by formula [I] except for special cases. Accordingly, compound [I] as mentioned herein is usually understood to include not only the free form but also an ester thereof and a salt thereof. The same applies not only to compound [I] but also to compound [I'], and to starting material compounds, e.g., compounds [II], [III], and [IV] below.

[0007] R^1 represents an amino group which may be protected. In the field of β-lactams and peptides, protective groups for amino groups have already been thoroughly investigated, with a method of amino group protection established. In the present invention, such commonly known protective groups can be used as appropriate to protect amino groups. Useful protective groups for amino groups include, for example, C_{1-6} alkanoyl groups which may be substituted, C_{3-5} alkenoyl groups which may be substituted, C_{6-10} aryl-carbonyl groups which may be substituted, heterocyclic carbonyl groups, C_{1-10} alkylsulfonyl groups which may be substituted, C_{6-10} arylsulfonyl groups which may be substituted, substituted oxycarbonyl groups, carbamoyl groups which may be substituted, thiocarbamoyl groups which may be substituted, C_{6-10} aryl-methyl groups which may be substituted, di-C_{6-10} aryl-methyl groups which may be substituted, tri-C_{6-10} aryl-methyl groups which may be substituted, C_{6-10} aryl-methylene groups which may be substituted, C_{6-10} arylthio groups which may be substituted, substituted silyl groups, 2-C_{1-10} alkoxy-carbonyl-1-methyl-1-ethenyl groups, and groups represented by the formula M'OCO- [wherein M' represents an alkali metal].

[0008] As "C_{1-6} alkanoyl groups which may be substituted," there may be used, for example, C_{1-6} alkanoyl groups which may be substituted by 1 to 3 substituents selected from among halogens, oxo, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{6-10} aryl, C_{6-10} aryloxy, C_{6-10} arylthio, etc. Specifically, there may be used, for example, formyl, acetyl, propionyl, butyryl, valeryl, pivaloyl, succinyl, glutaryl, monochloroacetyl, dichloroacetyl, trichloroacetyl, monobromoacetyl, monofluoroacetyl, difluoroacetyl, trifluoroacetyl, monoiodoacetyl, acetacetyl, 3-oxobutyryl, 4-chloro-3-oxobutyryl, phenylacetyl, p-chlorophenylacetyl, phenoxyacetyl, and p-chlorophenoxyacetyl. As "C_{3-5} alkenoyl groups which may be substituted," there may be used, for example, C_{3-5} alkenoyl groups which may be substituted by 1 to 3 substituents selected from among halogens, C_{6-10} aryl, etc. Specifically, there may be used, for example, acryloyl, crotonoyl, maleoyl, cinnamoyl, p-chlorocinnamoyl, and β-phenylcinnamoyl. As "C_{6-10} aryl-carbonyl groups which may be substituted," there may be used, for example, C_{6-10} aryl-carbonyl groups which may be substituted by 1 to 3 substituents selected from among halogens, nitro, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, etc. Specifically, there may be used, for example, benzoyl, naphthoyl, phthaloyl, p-toluoyl, p-tert-butylbenzoyl, p-hydroxybenzoyl, p-methoxybenzoyl, p-tert-butoxybenzoyl, p-chlorobenzoyl, and p-nitrobenzoyl.

[0009] "Heterocyclic groups" in "heterocyclic carbonyl groups" refer to groups resulting from the removal of one hydrogen atom bound to a carbon atom of a heterocyclic ring. Such heterocyclic rings include, for example, 5- to 8-membered rings containing 1 to several, preferably 1 to 4 hetero atoms such as nitrogen atoms (may be oxidated), oxygen atoms, and sulfur atoms, or condensed rings thereof. Specifically, such

heterocyclic groups are exemplified by 2- or 3-pyrrolyl; 3-, 4- or 5-pyrazolyl; 2-, 4- or 5-imidazolyl; 1,2,3- or 1,2,4-triazolyl; 1H- or 2H-tetrazolyl; 2- or 3-furyl; 2- or 3-thienyl; 2-, 4- or 5-oxazolyl; 3-, 4- or 5-isoxazolyl; 1,2,3-oxadiazol-4-yl or 1,2,3-oxadiazol-5-yl; 1,2,4-oxadiazol-3-yl or 1,2,4-oxadiazol-5-yl; 1,2,5- or 1,3,4-oxadiazolyl; 2-, 4- or 5-thiazolyl; 3-, 4- or 5-isothiazolyl; 1,2,3-thiadiazol-4-yl or 1,2,3-thiadiazol-5-yl; 1,2,4-thiadiazol-3-yl or 1,2,4-thiadiazol-5-yl; 1,2,5- or 1,3,4-thiadiazolyl; 2- or 3-pyrrolidinyl; 2-, 3- or 4-pyridyl; 2-, 3- or 4-pyridyl-N-oxide; 3- or 4-pyridazinyl; 3- or 4-pyridazinyl-N-oxide; 2-, 4- or 5-pyrimidinyl; 2-, 4- or 5-pyrimidinyl-N-oxide; pyrazinyl; 2-, 3- or 4-piperidinyl; piperazinyl; 3H-indol-2-yl or 3H-indol-3-yl; 2-, 3- or 4-pyranyl; 2-, 3- or 4-thiopyranyl; benzopyranyl; quinolyl; pyrido[2,3-d]pyrimidyl; 1,5-, 1,6-, 1,7-, 1,8-, 2,6- or 2,7-naphthylidyl; thieno[2,3-d]pyridyl; pyrimidopyridyl; pyrazinoquinolyl; and benzopyranyl. As "C_{1-10} alkylsulfonyl groups which may be substituted," there may be used, for example, C_{1-10} alkylsulfonyl groups which may be substituted by 1 to 3 substituents selected from among halogens, C_{6-10} aryl, C_{6-10} aryloxy, etc. Specifically, there may be used, for example, methanesulfonyl, ethanesulfonyl, and camphorsulfonyl.

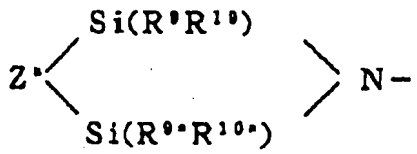
[0010] As "C_{6-10} arylsulfonyl groups which may be substituted," there may be used, for example, C_{6-10} arylsulfonyl groups which may be substituted by 1 to 3 substituents selected from among halogens, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, etc. Specifically, there may be used, for example, benzenesulfonyl, naphthalenesulfonyl, p-toluenesulfonyl, p-tert-butylbenzenesulfonyl, p-methoxybenzenesulfonyl, p-chlorobenzenesulfonyl, and p-nitrobenzenesulfonyl. As "substituted oxycarbonyl groups," there may be used, for example, C_{1-10} alkoxy-carbonyl groups, C_{3-10} cycloalkyloxy-carbonyl groups, C_{5-10} crosslinked cyclic hydrocarbon oxy-carbonyl groups, C_{2-10} alkenyloxy-carbonyl groups, C_{6-10} aryloxy-carbonyl groups or C_{7-19} aralkyloxy-carbonyl groups, including those having 1 to 3 substituents selected from among C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-10} alkanoyloxy, C_{1-10} alkoxy-carbonyloxy, C_{3-10} cycloalkyloxy-carbonyloxy, substituted silyl groups (substituted silyl groups mentioned below, e.g., trimethylsilyl, tert-butyldimethylsilyl), C_{1-6} alkylsulfonyl, halogens, cyano, C_{1-6} alkyl, nitro, etc. Specifically, there may be used, for example, methoxymethyloxycarbonyl, acetylmethyloxycarbonyl, 2-trimethylsilylethoxycarbonyl, 2-methanesulfonylethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-cyanoethoxycarbonyl, aryloxycarbonyl, p-methylphenoxycarbonyl, p-methoxyphenoxycarbonyl, p-chlorophenoxycarbonyl, m-nitrophenoxycarbonyl, p-methylbenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, and 3, 4-dimethoxy-6-nitrobenzyloxycarbonyl.

[0011] As "carbamoyl groups which may be substituted," there may be used, for example, carbamoyl groups which may be substituted by 1 or 2 substituents selected from among C_{1-6} alkyl, C_{6-10} aryl, C_{1-6} alkanoyl, C_{6-10} arylcarbonyl, C_{1-6} alkoxy-phenyl groups, etc. Specifically, there may be used, for example, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-phenylcarbamoyl, N-acetylcarbamoyl, N-benzoylcarbamoyl, and N-(p-methoxyphenyl)carbamoyl.
As "thiocarbamoyl groups which may be substituted," there may be used, for example, thiocarbamoyl groups which may be substituted by 1 or 2 substituents selected from among C_{1-6} alkyl, C_{6-10} aryl, etc., exemplified by thiocarbamoyl, N-methylthiocarbamoyl, and N-phenylthiocarbamoyl.

[0012] As "C_{6-10} aryl-methyl groups which may be substituted," there may be used, for example, C_{6-10} aryl-methyl groups which may be substituted by 1 to 3 substituents selected from among halogens, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, etc. Specifically, there may be used, for example, benzyl, naphthylmethyl, p-methylbenzyl, p-methoxybenzyl, p-chlorobenzyl, and p-nitrobenzyl. As "di-C_{6-10} aryl-methyl groups which may be substituted," there may be used, for example, di-C_{6-10} aryl-methyl groups which may be substituted by 1 to 3 substituents selected from among halogens, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, etc.

Specifically, there may be used, for example, benzhydryl and di(p-tolyl)methyl. As "tri-C_{6-10} aryl-methyl groups which may be substituted," there may be used, for example, tri-C_{6-10} aryl-methyl groups which may be substituted by 1 to 3 substituents selected from among halogens, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, etc. Specifically, there may be used, for example, trityl and tri(p-tolyl)methyl. As "C_{6-10} aryl-methylene groups which may be substituted," there may be used, for example, C_{6-10} aryl-methylene groups which may be substituted by 1 to 3 substituents selected from among halogens, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, etc. Specifically, there may be used, for example, benzylidene, p-methylbenzylidene, and p-chlorobenzylidene. As "C_{6-10} arylthio groups which may be substituted," there may be used, for example, C_{6-10} arylthio groups which may be substituted by 1 to 3 substituents selected from among halogens, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, etc. Specifically, there may be used, for example, o-nitrophenylthio.

[0013] A "substituted silyl group" cooperates with a protected amino group to form a group represented by the formula $R^6R^7R^8SiNH$-, $(R^6R^7R^8Si)_2N$- or
[Formula 14]



[wherein each of R^6, R^7, R^8, R^9, R^{10}, R^{9a} and R^{10a} represents a C_{1-6} alkyl group or a C_{6-10} aryl group; Z^a represents a C_{1-3} alkylene group (methylene, ethylene, propylene, etc.)]. Preferable examples of "substituted silyl groups" include, for example, trimethylsilyl, tert-butyldimethylsilyl, and -$Si(CH_3)_2CH_2CH_2Si(CH_3)_2$-. As "2-$C_{1-10}$ alkoxy-carbonyl-1-methyl-1-ethenyl groups," there may be used, for example, 2-methoxycarbonyl-1-methyl-1-ethenyl, 2-ethoxycarbonyl-1-methyl-1-ethenyl, and 2-tert-butoxycarbonyl-1-methyl-1-ethenyl. The "alkali metal" represented by M' is preferably sodium or potassium, for example, with greater preference given to sodium etc. Judging from antibacterial activity, R^1 is preferably an amino group.

[0014] R^2 represents a hydrogen atom or a group bound via a carbon atom. The "group bound via a carbon atom" represented by R^2 is preferably a hydrocarbon group which may be substituted (e.g., alkyl groups which may be substituted, alkenyl groups which may be substituted, alkinyl groups which may be substituted, aralkyl groups which may be substituted, cyclic hydrocarbon groups which may be substituted), an acyl group or a non-aromatic heterocyclic group which has a bond at a carbon atom, and which may be substituted, for example, with greater preference given to alkyl groups which may be substituted, alkenyl groups which may be substituted, cyclic hydrocarbon groups which may be substituted, etc. "Alkyl groups" in "alkyl groups which may be substituted" are preferably C_{1-6} alkyl groups etc., with greater preference given to methyl, ethyl, isopropyl, etc. "Alkenyl groups" in "alkenyl groups which may be substituted" are preferably C_{2-6} alkenyl groups etc. "Alkinyl groups in "alkinyl groups which may be substituted" are preferably C_{2-6} alkinyl groups etc. "Aralkyl groups" in "aralkyl groups which may be substituted" are preferably C_{7-19} aralkyl groups etc. As "cyclic hydrocarbon groups" in "cyclic hydrocarbon groups which may be substituted," there may be mentioned, for example, 3- to 7-membered non-aromatic cyclic hydrocarbon groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, and 3-cyclohexen-1-yl, with greater preference given to C_{3-7} cycloalkyl groups such as cyclobutyl and cyclopentyl. As "acyl groups," there may be mentioned, for example, "C_{1-6} alkanoyl groups which may be substituted," "C_{3-5} alkenoyl

groups which may be substituted," "C_{6-10} aryl-carbonyl groups which may be substituted," and "heterocyclic carbonyl groups," which are mentioned above to exemplify protective groups for the "amino group which may be protected" represented by R^1. "Non-aromatic heterocyclic groups" in "non-aromatic heterocyclic groups which have a bond at a carbon atom, and which may be substituted" are preferably 3- to 6-membered non-aromatic heterocyclic groups containing 1 or 2 hetero atoms such as nitrogen atoms, oxygen atoms, and sulfur atoms, in addition to carbon atoms, e.g., oxilanyl, azetidinyl, oxethanyl, thiethanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, and thiomorpholinyl.

[0015] As substituents which may be present in the aforementioned "hydrocarbon group," there may be mentioned, for example, heterocyclic groups, hydroxyl groups, C_{1-6} alkoxy groups, C_{3-10} cycloalkyl, C_{3-7} cycloalkyloxy groups, C_{6-10} aryloxy groups, C_{7-19} aralkyloxy groups, heterocyclic oxy groups, mercapto groups, C_{1-6} alkylthio groups, C_{3-10} cycloalkylthio groups, C_{6-10} arylthio groups, C_{7-19} aralkylthio groups, heterocyclic thio groups, amino groups, mono-C_{1-6} alkylamino groups, di-C_{1-6} alkylamino groups, tri-C_{1-6} alkylammonium groups, C_{3-10} cycloalkylamino groups, C_{6-10} arylamino groups, C_{7-19} aralkylamino groups, heterocyclic amino groups, cyclic amino groups, azide groups, nitro groups, halogen atoms, cyano groups, carboxyl groups, C_{1-10} alkoxy-carbonyl groups, C_{6-10} aryloxy-carbonyl groups, C_{7-19} aralkyloxy-carbonyl groups, C_{6-10} aryl-carbonyl groups, C_{1-6} alkanoyl groups, C_{3-5} alkenoyl group, C_{6-10} aryl-carbonyloxy groups, C_{2-6} alkanoyloxy groups, C_{3-5} alkenoyloxy groups, carbamoyl groups which may be substituted, thiocarbamoyl groups which may be substituted, carbamoyloxy groups which may be substituted, phthalimide groups, C_{1-6} alkanoylamino groups, C_{6-10} aryl-carbonylamino groups, C_{1-10} alkoxy-carboxamide groups, C_{6-10} aryloxy-carboxamide groups, and C_{7-19} aralkyloxy-carboxamide groups; 1 to 4 of these substituents, whether identical or not, may be present.

[0016] As "carbamoyl groups which may be substituted" mentioned to exemplify substituents for the aforementioned "hydrocarbon group," there may be used, for example, carbamoyl groups which may be substituted by 1 or 2 substituents selected from among C_{1-6} alkyl groups, C_{6-10} aryl groups, C_{1-6} alkanoyl groups, C_{6-10} arylcarbonyl groups, C_{1-6} alkoxy-phenyl groups, etc., and cyclic aminocarbonyl groups. Specifically, there may be used, for example, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-phenylcarbamoyl, N-acetylcarbamoyl, N-benzoylcarbamoyl, N-(p-methoxyphenyl)carbamoyl, pyrrolidinocarbonyl, piperidinocarbonyl, piperazinocarbonyl, and morpholinocarbonyl. As "thiocarbamoyl groups which may be substituted," there may be used, for example, thiocarbamoyl groups which may be substituted by 1 or 2 substituents selected from among C_{1-6} alkyl groups, C_{6-10} aryl groups, etc., exemplified by thiocarbamoyl, N-methylthiocarbamoyl, and N-phenylthiocarbamoyl. As "carbamoyloxy groups which may be substituted," there may be used, for example, carbamoyloxy groups which may be substituted by 1 or 2 substituents selected from among C_{1-6} alkyl groups, C_{6-10} aryl groups, etc. Specifically, there may be used, for example, carbamoyloxy, N-methylcarbamoyloxy, N,N-dimethylcarbamoyloxy, N-ethylcarbamoyloxy, and N-phenylcarbamoyloxy.

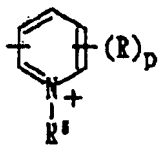
[0017] As heterocyclic groups in heterocyclic groups, heterocyclic oxy groups, heterocyclic thio groups and heterocyclic amino groups as substituents for the "hydrocarbon group," there may be used the same groups as heterocyclic groups in the aforementioned "heterocyclic carbonyl group." As substituents which may be present in the "alkyl groups" in the aforementioned "alkyl group which may be substituted," the "alkenyl group" in the "alkenyl group which may be substituted," the "aralkyl group" in the "aralkyl group which may be substituted," and the "cyclic hydrocarbon group" in the "cyclic hydrocarbon group which may be substituted," there may be used, for example, the same groups as substituents which may be present

in the "hydrocarbon group" in the aforementioned "hydrocarbon group which may be substituted." As substituents for the aforementioned "non-aromatic heterocyclic group which has a bond at a carbon atom, and which may be substituted," there may be mentioned the hydrocarbon groups and substituents therefor mentioned to exemplify substituents for the aforementioned "hydrocarbon group which may be substituted."

[0018] R^2 is preferably a "hydrocarbon group which may be substituted" or the like. As such hydrocarbon groups, there may be mentioned, for example, C_{1-6} alkyl groups which may be substituted by 1 to 3 substituents selected from among hydroxyl groups, C_{3-10} cycloalkyl groups, C_{1-6} alkoxy groups, C_{1-6} alkylthio groups, amino groups, halogen atoms, carboxyl groups, C_{1-10} alkoxycarbonyl groups, carbamoyl groups which may be substituted, cyano groups, azide groups, heterocyclic groups, etc. Specifically, there may be mentioned cyclopropylmethyl, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 1-ethoxyethyl, 2-hydroxyethyl, methylthiomethyl, 2-aminoethyl, fluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, chloromethyl, 2-chloroethyl, 2,2-dichloroethyl, 2,2,2-trichloroethyl, 2-bromoethyl, 2-iodoethyl, 2,2,2-trifluoroethyl, carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 2-carboxypropyl, 3-carboxypropyl, 1-carboxybutyl, cyanomethyl, 1-carboxy-1-methylethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl, 1-methoxycarbonyl-1-methylethyl, 1-ethoxycarbonyl-1-methylethyl, 1-tert-butoxycarbonyl-1-methylethyl, 1-benzyloxycarbonyl-1-methylethyl, 1-pivaloyloxycarbonyl-1-methylethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, 2-azidoethyl, 2-(pyrazolyl)ethyl, 2-(imidazolyl)ethyl, 2-(2-oxopyrrolidin-3-yl)ethyl, 1-carboxy-1-(2,3,4-trihydroxyphenyl)methyl, etc. The most preferable for R^2 is exemplified by linear or branched C_{1-6} alkyl groups which may be substituted by 1 to 3 substituents selected from among halogens, hydroxyl groups, C_{1-6} alkoxy groups, carboxyl groups, C_{1-10} alkoxycarbonyl groups, cyano groups, and carbamoyl groups, such as methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, fluoromethyl, 2-fluoroethyl, 2-chloroethyl, 2-hydroxyethyl, 2-methoxyethyl, cyanomethyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, carbamoylmethyl, N-methylcarbamoylmethyl, and N,N-dimethylcarbamoylmethyl; C_{3-5} cycloalkyl groups such as cyclopropyl, cyclobutyl, and cyclopentyl; and C_{3-5} cycloalkyl-C_{1-3} alkyl groups such as cyclopropylmethyl. C_{1-6} alkyl groups which may be substituted and C_{3-5} cycloalkyl groups are particularly preferable.

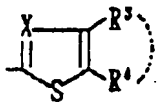
[0019] One of R^3 and R^4 represents a pyridinium group which may be substituted, the other representing a hydrogen atom or a hydrocarbon group which may be substituted, or R^3 and R^4 may bind together to form a heterocyclic ring which contains a quaternized nitrogen atom, and which may be substituted. As the "pyridinium group which may be substituted," there may be used, for example, a group represented by the formula:

[Formula 15]

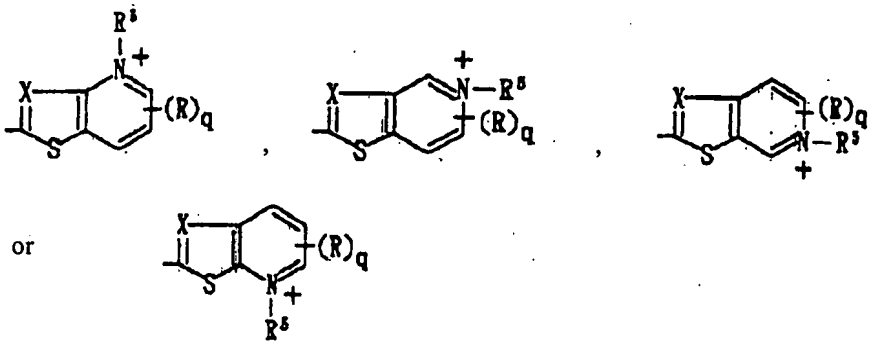


[wherein R^5 represents a hydrocarbon group which may be substituted; R represents a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxy-carbonyl group, amino, nitro, halogen or carboxy; p represents an integer from 0 to 4]. Provided that R^3 and R^4 bind together to form a heterocyclic ring which contains a quaternized nitrogen atom, and which may be substituted, the group represented by the formula:

[Formula 16]



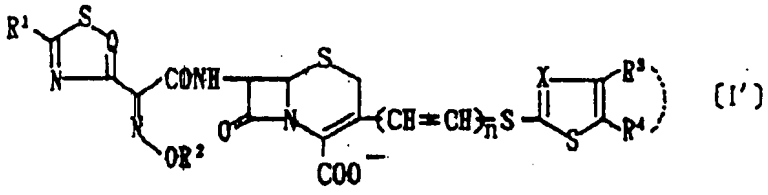
is exemplified by 6-membered unsaturated heterocyclic rings represented by the formula:



[wherein q represents an integer from 0 to 3; the other symbols have the same definitions as those given above]. As the "hydrocarbon group which may be substituted" represented by R^3, R^4 or R^5, there may be used the same groups as "hydrocarbon groups which may be substituted" mentioned to exemplify the "group bound via a carbon atom" represented by R^2. Each of p and q is preferably 0. R^5 is preferably a C_{1-4} alkyl group such as methyl, or the like. Regarding R^3 and R^4, preference is given to a case wherein R^3 is a pyridinium group which may be substituted and R^4 is a hydrogen atom, or wherein R^3 and R^4 bind together to form a 6-membered unsaturated heterocyclic ring containing a quaternized nitrogen atom, and the like.

[0020] Each of Q and X represents a nitrogen atom or CH. Each of Q and X is preferably a nitrogen atom. Y represents S, O or CH_2. Y is preferably S. Accordingly, compound [I] is preferably a compound represented by [I']:

[Formula 17]



(I')

[wherein the symbols have the same definitions as those given above], or an ester thereof or a salt thereof. n represents 0 or 1 and is preferably 1.

[0021]

[Formula 18]

With respect to compound [I] above, on the right shoulder of the 4-position -COO is a carboxylate anion from a carboxyl group, forming an intramolecular salt in cooperation with the positive charge on the 3-position heterocyclic ring (hereinafter also referred to as A^+) in compound [I]. On the other hand, compound [I] may form a pharmacologically acceptable ester or salt. Useful pharmacologically acceptable salts include inorganic base salts, ammonium salts, organic base salts, inorganic acid adduct salts, organic

acid adduct salts, and basic amino acid salts. As inorganic bases capable of forming inorganic base salts, there may be used, for example, alkali metals (e.g., sodium, potassium) and alkaline earth metals (e.g., calcium). As organic bases capable of forming organic base salts, there may be used, for example, procaine, 2-phenylethylbenzylamine, dibenzylethylenediamine, ethanolamine, diethanolamine, trishydroxymethylaminomethane, polyhydroxyalkylamine, and N-methylglucosamine. As inorganic acids capable of forming inorganic acid adduct salts, there may be used, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid. As organic acids capable of forming organic acid adduct salts, there may be used, for example, p-toluenesulfonic acid, methanesulfonic acid, formic acid, trifluoroacetic acid, and maleic acid. As basic amino acids capable of forming basic amino acid salts, there may be used, for example, lysine, arginine, ornithine, and histidine. Of these salts, basic salts (i.e., inorganic base salts, ammonium salts, organic base salts, basic amino acid salts) mean acid adduct salts capable of being formed in the presence of a basic group such as an amino group, a mono-alkylamino group, a dialkylamino group, a cycloalkylamino group, an arylamino group, an aralkylamino group, a cyclic amino group, or a nitrogen-containing heterocyclic group in the substituent R^1, R^2, or R^5 of compound [I]. Such acid adduct salts include a salt represented by the formula:
[Formula 19]

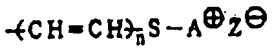
wherein 1 mol of acid is added to the moiety at which an intramolecular salt is formed in compound [I], i.e., the 4-position carboxylate moiety (COO^-) and 3-position $(CH=CH)_n S\text{-}A^+$ moiety, to form a 4-position carboxyl group (COOH) and 3-position $(CH=CH)_n S\text{-}A^+Z^-$ [wherein Z^- represents an anion resulting from the removal of proton H^+ from an inorganic acid or organic acid, e.g., chloride ion, bromide ion, sulfate ion, p-toluenesulfonate ion, methanesulfonate ion, trifluoroacetate ion]. An ester derivative of compound [I] means an ester capable of being formed by esterifying a carboxyl group in the molecule, and is an ester which can be used as a synthesis intermediate, and which is metabolically unstable and non-toxic. As esters which can be used as synthesis intermediates, there may be used $C_{1\text{-}6}$ alkyl esters which may be substituted, $C_{2\text{-}6}$ alkenyl esters, $C_{3\text{-}10}$ cycloalkyl esters, $C_{3\text{-}10}$ cycloalkyl-$C_{1\text{-}6}$ alkyl esters, $C_{6\text{-}10}$ aryl esters which may be substituted, $C_{7\text{-}12}$ aralkyl esters which may be substituted, di-$C_{6\text{-}10}$ aryl-methyl esters, tri-$C_{6\text{-}10}$ aryl-methyl esters, substituted silyl esters, etc.

[0022] As "$C_{1\text{-}6}$ alkyl esters which may be substituted," there may be used, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, and n-hexyl; these esters may be substituted by 1 to 3 substituents such as benzyloxy, $C_{1\text{-}4}$ alkylsulfonyl (e.g., methylsulfonyl), trimethylsilyl, halogens (e.g., fluorine, chlorine, bromine), acetyl, nitrobenzoyl, mesylbenzoyl, phthalimide, succinimide, benzenesulfonyl, phenylthio, di-$C_{1\text{-}4}$ alkylamino (e.g., dimethylamino), pyridyl, $C_{1\text{-}4}$ alkylsulfinyl (e.g., methylsulfinyl), and cyano. Specifically, as such groups, there may be used, for example, benzyloxymethyl, 2-methylsulfonylethyl, 2-trimethylsilylethyl, 2,2,2-trichloroethyl, 2-iodoethyl, acetylmethyl, p-nitrobenzoylmethyl, p-mesylbenzoylmethyl, phthalimidomethyl, succinimidomethyl, benzenesulfonylmethyl, phenylthiomethyl, dimethylaminoethyl, pyridin-1-oxide-2-methyl, methylsulfinyl-methyl, and 2-cyano-1,1-dimethylethyl. As $C_{2\text{-}6}$ alkenyl groups which form "$C_{2\text{-}6}$ alkenyl esters," there may be used vinyl, aryl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, methallyl, 1,1-dimethylaryl, 3-methyl-3-butenyl, etc.

[0023] As $C_{3\text{-}10}$ cycloalkyl groups which form "$C_{3\text{-}10}$ cycloalkyl esters," there may be used cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, etc. As $C_{3\text{-}10}$ cycloalkyl-$C_{1\text{-}6}$ alkyl groups which form "$C_{3\text{-}10}$ cycloalkyl-$C_{1\text{-}6}$ alkyl esters," there may be used cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, etc. As "$C_{6\text{-}10}$ aryl groups" which form "$C_{6\text{-}10}$ aryl esters which may

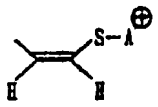
be substituted," there may be used, for example, phenyl, α-naphthyl, β-naphthyl, and biphenyl; these groups may be substituted by 1 to 3 substituents such as nitro and halogens (e.g., fluorine, chlorine, bromine). Specifically, as such groups, there may be used, for example, p-nitrophenyl and p-chlorophenyl.

[0024] As "C_{7-12} aralkyl groups" which form "C_{7-12} aralkyl esters which may be substituted," there may be used, for example, benzyl, 1-phenylethyl, 2-phenylethyl, phenylpropyl, and naphthylmethyl; these groups may be substituted by 1 to 3 substituents such as nitro, C_{1-4} alkoxy (e.g., methoxy), C_{1-4} alkyl (e.g., methyl, ethyl), and hydroxy. Specifically, as such groups, there may be used, for example, p-nitrobenzyl, p-methoxybenzyl, and 3,5-di-tert-butyl-4-hydroxybenzyl. As di-C_{6-10} aryl-methyl groups which form "di-C_{6-10} aryl-methyl esters," there may be used benzhydryl etc. As tri-C_{6-10} aryl-methyl groups which form tri-C_{6-10} aryl-methyl esters, there may be used trityl etc. As substituted silyl groups which form substituted silyl esters, there may be used trimethylsilyl, tert-butyldimethylsilyl, and $-Si(CH_3)_2CH_2CH_2Si(CH_3)_2-$. The aforementioned esters include 4-position esters. Compounds having an aforementioned ester group at the 4-position as described above have a salt with a group represented by the formula:
[Formula 20]



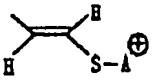
[wherein the symbols have the same definitions as those given above] formed at the 3-position.

[0025] The present invention includes pharmacologically acceptable compounds which are converted to compound in the living body, as well as the aforementioned ester derivatives. When n=1 in compound [I] of the present invention and the starting material compound, the cis-isomer (Z-configuration), trans-isomer (E-configuration), and cis-trans mixtures are included. Compound [I] of the present invention is preferably in the form of the trans-isomer (E-configuration). With respect to compound [I], the cis-isomer (Z-configuration), for example, means one of the geometric isomers having a partial structure represented by formula [XVII]:
[Formula 21]



[XVII]

and the trans-isomer means a geometric isomer having a partial structure represented by formula [XVIII]:
[Formula 22]



[XVIII]

[0026] Unless otherwise specified herein, individual substituents are exemplified as follows:
halogens: fluoro, chloro, bromo, iodo, etc.;
C_{1-4} alkyl groups: methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, etc.;
C_{1-6} alkyl groups: aforementioned C_{1-4} alkyl groups and pentyl, 2,2-dimethylpropyl, hexyl, etc.;
C_{2-6} alkenyl groups: vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, methallyl, 1,1-dimethylallyl, etc.;
C_{2-6} alkinyl group: etinyl, 1-propinyl, 2-propinyl, 2-butinyl, 2-pentinyl, 2-hexinyl, etc.;

C_{3-5} cycloalkyl groups: cyclopropyl, cyclobutyl, cyclopentyl, etc.;
C_{3-10} cycloalkyl groups: aforementioned C_{3-5} cycloalkyl groups and cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, etc.;
C_{6-10} aryl groups: phenyl, naphthyl, etc.;
C_{7-20} aralkyl groups: benzyl, 1-phenylethyl, 2-phenylethyl, phenylpropyl, naphthylmethyl, benzhydryl, etc.;

[0027] C_{1-10} alkoxy-carbonyloxy groups: methoxycarbonyloxy, ethoxycarbonyloxy, tert-butoxycarbonyloxy, etc.;
C_{1-6} alkoxy group: methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, 2,2-dimethylpropyloxy, hexyloxy, etc.;
C_{3-7} cycloalkyloxy groups: cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, etc.;
C_{6-10} aryloxy groups: phenoxy, naphthyloxy, etc.;
C_{7-19} aralkyloxy groups: benzyloxy, 1-phenylethyloxy, 2-phenylethyloxy, benzhydryloxy, etc.;

[0028] C_{1-6} alkylthio groups: methylthio, ethylthio, propylthio, butylthio, isobutylthio, t-butylthio, pentylthio, 2,2-dimethylpropylthio, hexylthio, etc.;
C_{3-10} cycloalkylthio groups: cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio, cycloheptylthio, cyclooctylthio, cyclodecylthio, etc.;
C_{6-10} arylthio groups: phenylthio, naphthylthio, etc.;
C_{7-19} aralkylthio groups: benzylthio, phenylethylthio, benzhydrylthio, tritylthio, etc.;
C_{1-4} alkylsulfinyl groups: methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, t-butylsulfinyl, etc.;
C_{1-6} alkylsulfonyl groups: methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, t-butylsulfonyl, pentylsulfonyl, 2,2-dimethylpropylsulfonyl, hexylsulfonyl, etc.;

[0029] Mono-C_{1-6} alkylamino groups: methylamino, ethylamino, n-propylamino, n-butylamino, etc.;
di-C_{1-4} alkylamino groups: dimethylamino, diethylamino, methylethylamino, di-(n-propyl)amino, di-(n-butyl)amino, etc.;
di-C_{1-6} alkylamino groups: aforementioned di-C_{1-4} alkylamino groups and di(pentyl)amino, di(n-hexyl)amino, etc.;
tri-C_{1-6} alkylammonium groups: trimethylammonium, etc.;
C_{3-10} cycloalkylamino groups: cyclopropylamino, cyclopentylamino, cyclohexylamino, etc.;
C_{6-10} arylamino groups: anilino, N-methylanilino, etc.;
C_{7-19} aralkylamino groups: benzylamino, 1-phenylethylamino, 2-phenylethylamino, benzhydrylamino, etc.;
cyclic amino groups: pyrrolidino, piperidino, piperazino, morpholino, 1-pyrrolyl, etc.;
C_{1-6} alkanoylamino groups: acetamide, propionamide, butyroamide, valeroamide, pivaroamide, etc.;
C_{6-10} allyl-carbonylamino groups: benzamide, naphthoylamide, phthalimide, etc.;

[0030] C_{1-6} alkanoyl groups: formyl, acetyl, propionyl, butyryl, valeryl, pivaloyl, succinyl, glutaryl, etc.;
C_{2-6} alkanoyloxy groups: acetoxy, propionyloxy, butyryloxy, valeryloxy, pivaloyloxy, etc.;
C_{1-10} alkanoyloxy groups: aforementioned C_{2-6} alkanoyloxy groups and formyloxy, hexanoyloxy, heptanoyloxy, etc.;
C_{3-5} alkenoyl group: acryloyl, crotonoyl, maleoyl, etc.;
C_{3-5} alkenoyloxy groups: acryloyloxy, crotonoyloxy, maleoyloxy, etc.;
C_{6-10} aryl-carbonyl groups: benzoyl, naphthoyl, phthaloyl, phenylacetyl, etc.;
C_{6-10} aryl-carbonyloxy groups: benzoyloxy, naphthoyloxy, phenylacetoxy, etc.;

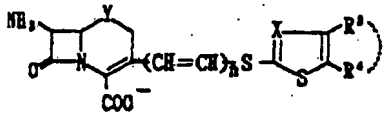
C_{1-6} alkoxy-phenyl groups: methoxyphenyl, ethoxyphenyl, propoxyphenyl, butoxyphenyl, t-butoxyphenyl, etc.;

[0031] C_{1-10} alkoxy-carbonyl groups: methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, 2,2-dimethylpropyloxycarbonyl, hexyloxycarbonyl, heptyloxycarbonyl, decyloxycarbonyl, etc.;
C_{1-10} alkoxy-carbonyloxy groups: methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, isopropoxycarbonyloxy, butoxycarbonyloxy, isobutoxycarbonyloxy, t-butoxycarbonyloxy, pentyloxycarbonyloxy, 2,2-dimethylpropyloxycarbonyloxy, hexyloxycarbonyloxy, heptyloxycarbonyloxy, decyloxycarbonyloxy, etc.;
C_{3-10} cycloalkyloxy-carbonyl groups: cyclopropyloxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl, cycloheptyloxycarbonyl, cyclooctyloxycarbonyl, cyclodecyloxycarbonyl, etc.;
C_{3-10} cycloalkyloxy-carbonyloxy groups: cyclopropyloxycarbonyloxy, cyclobutyloxycarbonyloxy, cyclopentyloxycarbonyloxy, cyclohexyloxycarbonyloxy, cycloheptyloxycarbonyloxy, cyclooctyloxycarbonyloxy, cyclodecyloxycarbonyloxy, etc.;

[0032] C_{5-10} crosslinked cyclic hydrocarbon oxy-carbonyl groups: norbornyloxycarbonyl, adamantyloxycarbonyl, etc.;
C_{2-10} alkenyloxy-carbonyl groups: allyloxycarbonyl etc.;
C_{6-10} aryloxy-carbonyl groups: phenoxycarbonyl, naphthyloxycarbonyl, etc.;
C_{7-19} aralkyloxy-carbonyl groups: benzyloxycarbonyl, benzhydryloxycarbonyl, etc.;
C_{1-10} alkoxy-carboxamide groups: methoxycarboxamide (CH_3OCONH-), ethoxycarboxamide, tert-butoxycarboxamide, etc.;
C_{6-10} aryloxy-carboxamide groups: phenoxycarboxamide (C_6H_5OCONH-), etc.;
C_{7-10} aralkyloxy-carboxamide groups: benzyloxycarboxamide ($C_6H_5CH_2OCONH$-), benzhydryloxycarboxamide, etc.;

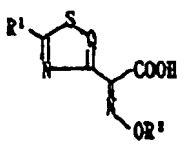
[0033] Production methods for compound [I] of the present invention are hereinafer described in detail.

Production method (1): Compound [I] can be synthesized by, for example, reacting a 7-amino compound represented by formula [II]:
[Formula 23]



[II]

[wherein the symbols have the same definitions as those given above], or an ester thereof or a salt thereof, and a carboxylic acid represented by formula [III]:
[Formula 24]



[III]

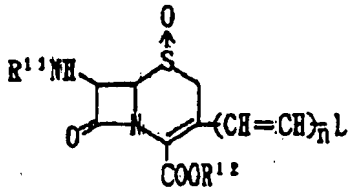
[wherein the symbols have the same definitions as those given above], or a salt thereof or a reactive

derivative thereof.

[0034] This method is a method wherein 7-amino compound [II] is acylated with carboxylic acid [III], or a salt thereof or a reactive derivative thereof. In this method, carboxylic acid [III] is used in the free form as is or a salt thereof or a reactive derivative as an acylating agent for the 7-position amino group of 7-amino compound [II]. Accordingly, free acid [III] or its inorganic base salt or organic base salt, or a reactive derivative such as an acid halide, an acid azide, an acid anhydride, a mixed acid anhydride, an active amide, an active ester, or an active thio ester is subjected to the acylating reaction. Inorganic base salts include alkali metal salts (e.g., sodium salt, potassium salt) and alkaline earth metal salts (e.g., calcium salt). Organic base salts include, for example, trimethylamine salt, triethylamine salt, tert-butyldimethylamine salt, dibenzylmethylamine salt, benzyldimethylamine salt, N,N-dimethylaniline salt, pyridine salt, and quinoline salt. Acid halides include, for example, acid chlorides and acid bromides. Mixed acid anhydrides include mono-C_{1-6} alkylcarbonic acid mixed acid anhydrides (e.g., mixed acid anhydrides of free acid [III] with monomethylcarbonic acid, monoethylcarbonic acid, monoisopropylcarbonic acid, monoisobutylcarbonic acid, mono-tert-butylcarbonic acid, monobenzylcarbonic acid, mono(p-nitrobenzyl)carbonic acid, monoallylcarbonic acid, etc.), C_{1-6} aliphatic carboxylic acid mixed acid anhydrides (e.g., mixed acid anhydrides of free acid [III] with acetic acid, trichloroacetic acid, cyanoacetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, isovaleric acid, pivalic acid, trifluoroacetic acid, trichloroacetic acid, acetoacetic acid, etc.), C_{7-12} aromatic carboxylic acid mixed acid anhydrides (e.g., mixed acid anhydrides of free acid [III] with benzoic acid, p-tolylic acid, p-chlorobenzoic acid, etc.), and organic sulfonic acid mixed acid anhydrides (e.g., mixed acid anhydrides of free acid [III] with methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.). Active amides include amides with nitrogen-containing heterocyclic compounds (e.g., acid amides of free acid [III] with pyrazole, imidazole, benzotriazole, etc.; these nitrogen-containing heterocyclic compounds may be substituted by C_{1-6} alkyl groups, C_{1-6} alkoxy groups, halogens, oxo groups, thioxo groups, C_{1-6} alkylthio groups, etc.). As active esters, there may be utilized all esters in use for this purpose in the field of β-lactam and peptide synthesis, including, for example, organic phosphoric acid esters (e.g., diethoxyphosphoric acid ester, diphenoxyphosphoric acid ester), as well as p-nitrophenyl ester, 2,4-dinitrophenyl ester, cyanomethyl ester, pentachlorophenyl ester, N-hydroxysuccinimide ester, N-hydroxyphthalimide ester, 1-hydroxybenzotriazole ester, 6-chloro-1-hydroxybenzotriazole ester, and 1-hydroxy-1H-2-pyridone ester. Active thio esters include esters with aromatic heterocyclic thiol compounds (e.g., 2-pyridylthiol ester, 2-benzothiazolylthiol ester; these heterocyclic rings may be substituted by C_{1-6} alkyl groups, C_{1-6} alkoxy groups, halogens, C_{1-6} alkylthio groups, etc.). On the other hand, 7-amino compound [II] is used in the free form as is, or a salt thereof or an ester thereof. Salts of 7-amino compound [II] include inorganic base salts, ammonium salts, organic base salts, inorganic acid adduct salts, and organic acid adduct salts. Inorganic base salts include alkali metal salts (e.g., sodium salt, potassium salt) and alkaline earth metal salts (e.g., calcium salt). Organic base salts include, for example, trimethylamine salt, triethylamine salt, tert-butyldimethylamine salt,dibenzylmethylamine salt, benzyldimethylamine salt, N,N-dimethylaniline salt, pyridine salt, and quinoline salt. Inorganic acid adduct salts include, for example, hydrochloride, hydrobromate, sulfate, nitrate, and phosphate. Organic acid adduct salts include formte, acetate, trifluoroacetate, methanesulfonate, and p-toluenesulfonate. As esters of 7-amino compound [II], there may be mentioned the same esters as those already mentioned to exemplify ester derivatives of compound [I]. Specifically, there may be mentioned C_{1-6} alkyl esters, C_{2-6} alkenyl esters, C_{3-10} cycloalkyl esters, C_{3-6} cycloalkyl-C_{1-6} alkyl esters, C_{6-10} aryl esters, C_{7-12} aralkyl esters, di-C_{6-10} arylmethyl esters, tri-C_{6-10} arylmethyl esters, and C_{2-6} alkanoyloxy-C_{1-6} alkyl esters. Starting material [III], a salt thereof, and a reactive derivative thereof can be easily produced using a commonly

known method (e.g., methods described in Japanese Unexamined Patent Publication kokai No. 60-231684 and kokai No. 62-149682, and elsewhere) or a method based thereon. A reactive derivative of compound [III] may be reacted with 7-amino compound [II] as isolated from the reaction mixture, or the reaction mixture containing a pre-isolated reactive derivative of compound [III] as is may be reacted with 7-amino compound [II]. When carboxylic acid [III] is used in the form of a free acid or a salt, an appropriate condensing agent is used. As condensing agents, there may be used N,N'-di-substitutional carbodiimides such as N,N'-dicyclohexylcarbodiimide; azolides such as N,N'-carbonyldiimidazole and N,N'-thiocarbonyldiimidazole; dehydrating agents such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride, and alkoxyacetylene; and 2-halogenopyridinium salts such as 2-chloropyridinium methyl iodide and 2-fluoropyridinium methyl iodide. When these condensing agents are used, the reaction is believed to proceed via a reactive derivative of carboxylic acid [III]. The reaction is usually carried out in a solvent which does not interfere with the reaction, and which is selected as appropriate. Such solvents include ethers such as dioxane, tetrahydrofuran, diethyl ether, tert-butyl methyl ether, diisopropyl ether, and ethylene glycol-dimethyl ether, esters such as ethyl formate, ethyl acetate, and n-butyl acetate, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, tricrene, and 1,2-dichloroethane, hydrocarbons such as n-hexane, benzene, and toluene, amides such as formamide, N,N-dimethylformamide, and N,N-dimethylacetamide, ketones such as acetone, methyl ethyl ketone, and methyl isobutyl ketone, nitriles such as acetonitrile and propionitrile, and dimethylsulfoxide, sulfolane, hexamethylphosphoramide, water, etc.; these substances may be used singly or as mixed solvents. The amount of acylating agent [III] used is normally about 1 to 5 mol, preferably about 1 to 3 mol, per mol of 7-amino compound [II]. The reaction is carried out over the temperature range from about -80 to 80°C, preferably about -40 to 50°C, and most preferably about -30 to 30°C. Reaction time varies depending on the kinds of 7-amino compound [II] and carboxylic acid [III], the kind of solvent (also mixing ratio in the case of a mixed solvent), reaction temperature, etc., and is normally about 1 minute to 72 hours, preferably about 15 minutes to 10 hours. When an acid halide is used as an acylating agent, the reaction may be carried out in the presence of a deacidifier for the purpose of removing the released hydrogen halide from the reaction system. Such deacidifiers include inorganic bases such as sodium carbonate, potassium carbonate, calcium carbonate, and sodium hydrogen carbonate, tertiary amines such as triethylamine, tri(n-propyl)
amine, tri(n-butyl)amine, diisopropylethylamine, cyclohexyldimethylamine, pyridine, lutidine, γ-collidine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, and N-methylmorpholine, and alkylene oxides such as propylene oxide and epichlorohydrine.

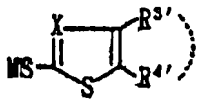
[0035] Of 7-amino compound [II] as a starting material for this reaction, a compound wherein Y=S, or an ester thereof or a salt thereof can, for example, be obtained as described below. First, a compound represented by formula [VII]:
[Formula 25]



[VII]

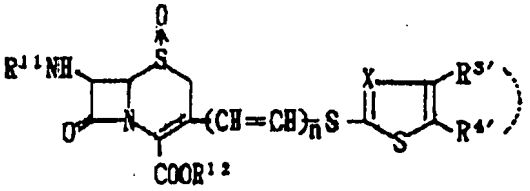
[wherein R^{11} represents a protective group for the amino group; R^{12} represents a protective group for the carboxyl group; L represents a halogen atom, a lower acyloxy group, or a sulfonyloxy group; the other

symbols have the same definitions as those given above], and a pyridine compound represented by formula [VIII]:
[Formula 26]



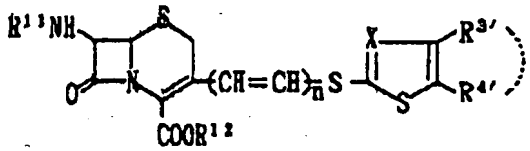
[VIII]

[wherein the symbols have the same definitions as those given above] or a salt thereof are reacted to yield a compound represented by formula [IX]:
[Formula 27]



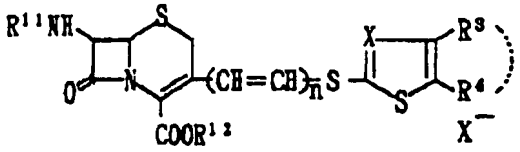
[IX]

[wherein the symbols have the same definitions as those given above] or a salt thereof, and subsequently, the S-oxide is reduced by, for example, the method described in Japanese Unexamined Patent Publication kokai No. 55-154978 and elsewhere, to yield a compound represented by formula [X]:
[Formula 28]



[X]

[wherein the symbols have the same definitions as those given above] or a salt thereof. Next, compound [X] is reacted with a compound which quaternizes a nitrogen atom in the pyridyl group which is represented by $R^{3'}$ or $R^{4'}$, and which may be substituted, or in the heterocyclic ring which is formed by $R^{3'}$ and $R^{4'}$ binding together, which contains a nitrogen atom, and which may be substituted (hereinafter referred to as quaternary ammoniating agent) to yield a compound represented by formula [XI]:
[Formula 29]



[XI]

[wherein the symbols have the same definitions as those given above]. Subsequently, by removing the protective group as necessary, compound [II] can be produced. The aforementioned quaternary ammoniating agent is exemplified by a compound represented by R^5-Z (R^5 has the same definition as that given above; Z represents a leaving group).

[0036] As protective groups for the carboxy group represented by R^{12}, there may be mentioned the aforementioned esters. Of particular preference are carboxy group protective groups which are in common use in the relevant field, and which are easy to remove, including tri(lower)alkylsilyl groups such as

trimethylsilyl groups, benzhydryl groups, p-methoxybenzyl groups, tert-butyl groups, p-nitrobenzyl groups, and phenacyl groups.

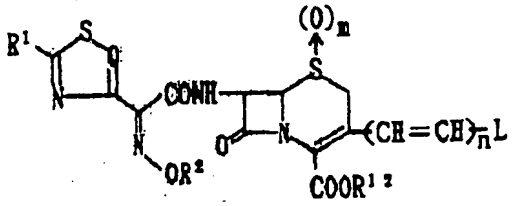
[0037] As protective groups for the amino group represented by R^{11}, there may be mentioned the aforementioned amino group protective groups. Of particular preference are tri(lower)alkylsilyl groups such as trimethylsilyl groups, acyl-series protective groups such as formyl groups, trifluoroacetyl groups, acetyl groups, tert-butoxycarbonyl groups, methoxyacetyl groups, benzyloxycarbonyl groups, and p-nitrobenzyloxycarbonyl groups, and aralkyl group-series protective groups such as benzyl groups, benzhydryl groups, and trityl groups. L is preferably a halogen atom such as chlorine, bromine, or iodine, an acyloxy group such as acetoxy, propionyloxy, butyryloxy, or 3-oxobutyryloxy, an alkylsulfonyloxy group such as methanesulfonyloxy or ethanesulfonyloxy, or an arylsulfonyloxy group such as benzenesulfonyloxy, naphthalenesulfonyloxy, p-toluenesulfonyloxy, p-tert-butylbenzenesulfonyloxy, p-methoxybenzenesulfonyloxy, p-chlorobenzenesulfonyloxy, or p-nitrobenzenesulfonyloxy. Of particular preference is a benzenesulfonyloxy or p-toluenesulfonyloxy group. Z represents a leaving group and is preferably a halogen atom such as chlorine, bromine, or iodine.

[0038] Compound [VIII] is also used in the form of a salt. Salts of compound [VIII] include, for example, alkali metal salts such as lithium salt, sodium salt, and potassium salt, and adduct salts with trialkylamines such as triethylamine and diisopropylamine. It is recommended that a nucleophilic substitution reaction of compound [VII] and compound [VIII] be normally carried out in an inert solvent. Such solvents include ketones such as acetone, halogenated hydrocarbons such as chloroform, dichloromethane, and dichloroethane, ethers such as diethyl ether, tetrahydrofuran, and dioxane, nitriles such as acetonitrile, alcohols such as methanol, ethanol, and n-propanol, amides such as dimethylformamide and dimethylacetamide, and sulfoxides such as dimethylsulfoxide. The amount of nucleophilic reagent [VIII] used is normally 1 to 5 mol, preferably about 1 to 3 mol per mol of compound [VII]. Reaction temperature is -30 to 120°C, preferably -20 to 80°C. The reaction is carried out for 5 minutes to 24 hours, preferably 15 to 10 hours. In addition, this reaction may be accelerated by the addition of a base or a salt. Such bases and salts include, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, and potassium carbonate, and organic amines like trialkylamines such as triethylamine and diisopropylethylamine. As salts, there may be used quaternary ammonium salts such as tetrabutylammonium salt.

[0039] The compound which is reacted with compound [X], and which is represented by R^5Z, is exemplified by C_{1-6} lower alkyl halides, C_{2-6} lower alkenyl halides, C_{2-6} lower alkinyl halides, hydroxy lower alkyl halides, carboxy lower alkyl halides, carbamoyl lower alkyl halides, and lower alkenoyl lower alkyl halides; such various halides include chloride, bromide, and iodide. It is recommended that the reaction of compound [X] and a quaternary ammoniating agent be normally carried out in an inert solvent; such solvents include halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride, aromatic hydrocarbons such as benzene, toluene, and xylene, ether fluids such as diethyl ether, tetrahydrofuran, and dioxane, nitriles such as acetonitrile, alcohols such as methanol, ethanol, and n-propanol, amides such as dimethylformamide and dimethylacetamide, and sulfoxides such as dimethylsulfoxide. The amount of quaternary ammoniating agent used is 1 to 50 mol, preferably 5 to 20 mol. Reaction temperature is 0 to 120°C, preferably 15 to 100°C. The reaction is carried out for 0.5 to 48 hours, preferably 1 to 24 hours. For example, when the protective group is a tri(lower)alkylsilyl group, the protective group can be removed from thus-obtained compound [XI] by treatment with water. When the protective group is a benzhydryl group, a trityl group, a p-methoxybenzyl group, a tert-butyl group, a tert-

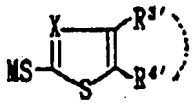
butoxycarbonyl group, a formyl group, or the like, it can be removed by treatment with formic acid, hydrochloric acid, trifluoroacetic acid, acetic acid, phenol, cresol, or the like. By the aforementioned deprotection reaction, 7-amino compound [II] wherein Y=S is obtained.

[0040] Compound [I] wherein Y=S can also be produced by, for example, production methods (2) and (3).
Production method (2): A production method for the compound described in (1) above characterized in that, for example, a compound represented by formula [XII]:
[Formula 30]



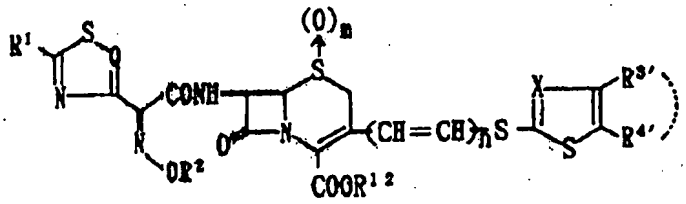
[XII]

[wherein m represents 0 or 1; the other symbols have the same definitions as those given above] and a compound represented by formula [VIII]:
[Formula 31]



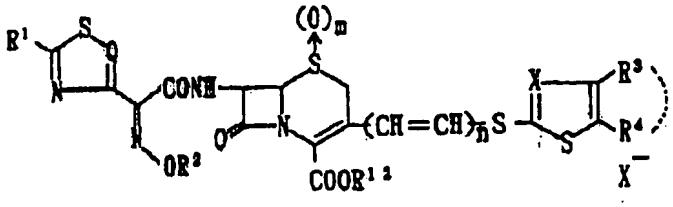
[VIII]

[wherein the symbols have the same definitions as those given above] are reacted to yield a compound represented by formula [XIII]:
[Formula 32]



[XIII]

[wherein the symbols have the same definitions as those given above], and the resulting compound is then reacted with a quaternary ammoniating agent to yield a compound represented by formula [XIV]:
[Formula 33]



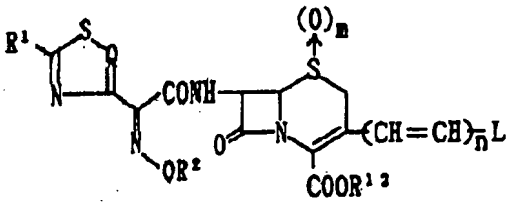
[XIV]

[wherein the symbols have the same definitions as those given above], and the protective group is removed.

[0041] The nucleophilic substitution reaction of compound [XII] and compound [VIII] can be carried out

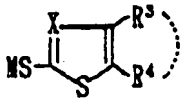
under the same reaction conditions as the reaction of compound [VII] and compound [VIII] in production method (1). The quaternary ammoniation of compound [XIII] can be carried out under the same reaction conditions as the reaction of compound [X] and a quaternary ammoniating agent in production method (1). Compound [XIV] thus obtained may have the protective group removed by the method described in production method (1), whereby the compound of formula [I] of the present invention is produced.

[0042] Production method (3): A production method for the compound described in (1) above characterized in that, for example, a compound represented by formula [XII]:
[Formula 34]



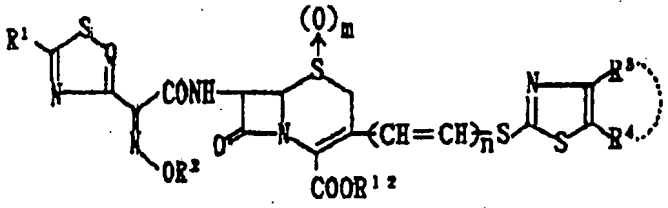
[XII]

[wherein the symbols have the same definitions as those given above] and a compound represented by formula [XV]:
[Formula 35]



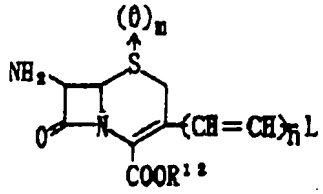
[XV]

[wherein the symbols have the same definitions as those given above] are reacted to yield a compound represented by formula [XIV]:
[Formula 36]



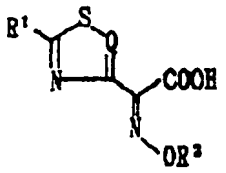
[wherein the symbols have the same definitions as those given above], and the protective group is removed. The reaction of compound [XII] and compound [XV] can be carried out under the same reaction conditions as the reaction of compound [VII] and compound [VIII] in production method (1). Compound [XIV] thus obtained may have the protective group removed by the method described in production method (1), whereby the compound of formula [I] of the present invention is produced.

[0043] Compound [XII] in this production method is produced by reacting a compound represented by formula [XVI]:
[Formula 37]



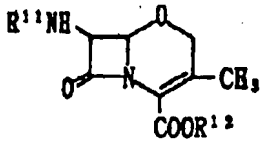
[XVI]

[wherein the symbols have the same definitions as those given above] and a carboxylic acid represented by formula [III]:
[Formula 38]



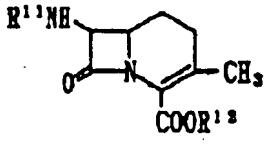
[III]

[wherein the symbols have the same definitions as those given above], or a salt thereof or a reactive derivative thereof in the same manner as production method (1). Furthermore, compound [XV] in this production method is produced by reacting compound [VIII] and a quaternary ammoniating agent under the same reaction conditions as the quaternary ammoniation reaction of compound [X] in production method (1). Compound [I] wherein Y=O or CH_2 is produced in accordance with production methods (1) through (3) using as a starting material a compound produced by the method described in, for example, Japanese Unexamined Patent Publication kokai No. 53-21188 and Tetrahedron Letters, Vol. 26, p. 3787 (1985), or a method based thereon, or using as a starting material a 3-methyloxacefem represented by formula [XIX]:
[Formula 39]



[XIX]

[wherein the symbols have the same definitions as those given above] which is produced by US4123528 and Heterocycles, Vol. 7, p. 839 (1977) or a method based thereon, or a 3-methylcarbacefem represented by formula [XX]:
[Formula 40]



[XX]

[wherein the symbols have the same definitions as those given above] which is produced by the method described in Japanese Unexamined Patent Publication kokai No. 55-154978 or a method based thereon. In the reactions of production methods (1) through (3) above, desired compound [I] of the present invention can be obtained by protective group removal and purification performed as necessary. Methods of protective group removal and purification methods are described below.

[0044] Methods of protective group removal: As described above, in the field of β-lactam and peptide synthesis, amino group protective groups have already been thoroughly investigated and methods of protection and methods of deprotection have already been established. In the present invention as well, protective group removal can be achieved using prior art methods as is. For example, monohalogenoacetyl groups (e.g., chloroacetyl, bromoacetyl) can be removed by means of thiourea, alkoxycarbonyl groups (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl) by means of acid (e.g., hydrochloric acid), aralkyloxycarbonyl groups (e.g., benzyloxycarbonyl, p-methylbenzyloxycarbonyl, p-nitrobenzyloxycarbonyl) by means of catalytic reduction, and 2,2,2-trichloroethoxycarbonyl by means of zinc and acid (e.g., acetic acid). On the other hand, when compound [I] has been esterified as a synthesis intermediate, the ester residue can be removed by a method known *per se* or a method based thereon. For example, 2-methylsulfonylethyl ester can be removed by means of alkali, aralkyl esters (e.g., benzyl ester, benzhydryl ester, p-methoxybenzyl ester, p-nitrobenzyl ester) by means of acid (e.g., trifluoroacetic acid) or catalytic reduction, 2,2,2-trichloroethyl ester by means of zinc and acid (e.g., acetic acid), and silyl esters (e.g., trimethylsilyl ester, tert-butyldimethylsilyl ester) by means of water alone. S-oxide reduction is achieved using a method established in the field of β-lactam. In the present invention as well, prior art methods can be utilized as is. For example, phosphorus trichloride and phosphorus tribromide are used.
Purification method for compound [I]: Using the various production methods described in detail in production methods (1) through (3) or, if necessary, by continuing any of the aforementioned method of protective group removal, compound [I] produced in the reaction mixture can be isolated and purified by means of commonly known means of treatment such as extraction, column chromatography, precipitation, and recrystallization. On the other hand, isolated compound [I] can also be converted to a desired physiologically acceptable salt using a commonly known method.

[0045] Compound [I] of the present invention possesses a broad spectrum of antibacterial activity, is low in toxicity, and can be used safely to prevent and treat various diseases caused by pathogenic bacteria in humans and mammalians (e.g., mice, rats, rabbits, dogs, cats, bovines, swines), e.g., airway infections and urinary tract infections. The antibacterial spectrum of antibacterial compound [I] is characterized as follows:

(1) Possesses very high activity against a wide variety of gram-negative bacteria.
(2) Possesses high activity against gram-positive bacteria (e.g., *Staphylococcus aureus*, *Corynebacterium diphtheriae*).
(3) Possesses high activity against methicillin-resistant *Staphylococcus aureus* (MRSA).
(4) Also possesses high activity against a variety of β-lactamase-producing gram-negative bacteria (e.g., *Escherichia* spp., *Enterobacter* spp, *Serratia* spp, *Proteus* spp.).

In addition, antibacterial compound [I] of the present invention is also featured by (1) excellent stability, (2) high blood concentrations, (3) long persistence of effect, (4) remarkable tissue transferability, etc.

[0046] Compound [I] of the present invention, like commonly known penicillins and cefalosporins, can be administered parenterally or orally in the form of injections, capsules, tablets, and granules (with preference given to injections). Regarding dosage, compound [I] may be administered in 2 to 3 divided doses in a day at 0.5 to 80 mg/day, preferably 2 to 40 mg/day per kg of body weight of the human or animal infected with a pathogenic bacterium mentioned above. When compound [I] is used as an injection, useful carriers include, for example, distilled water and physiological saline. When compound [I] is used as capsules, powders, granules, or tablets, it is used in mixture with commonly known pharmacologically acceptable excipients (e.g., starch, lactose, sucrose, calcium carbonate, calcium phosphate), binders (e.g., starch, gum

arabic, carboxymethyl cellulose, hydroxypropyl cellulose, crystalline cellulose), lubricants (e.g., magnesium stearate, talc), and disintegrants (e.g., carboxymethylcalcium, talc). The pharmaceutical composition and antibacterial composition as used herein may be compound [I] alone, or may contain carriers etc. as described above, and may contain appropriate amounts of other antibacterial compounds etc. as necessary.

[0047]
[Modes of Embodiment of the Invention]
The present invention is hereinafter described in more detail by means of the following reference examples, working examples, and test examples, which examples serve solely for exemplification and are not construed as limitative on the present invention, and may be varied as long as the scope of the present invention is not deviated from. Elution in column chromatography in reference examples and working examples was achieved with observation by TLC (thin layer chromatography). TLC observations were made using the $60F_{254}$ TLC plate produced by Merck Company in combination with the same solvent as that used as the elution solvent for column chromatography as the developing solvent, and an UV detector as the method of detection. The silica gel for column used was Kiesel Gel 60 (70 - 230 mesh) produced by Merck. "Sephadex" is a product of Pharmacia Fine Chemicals Company. XAD-2 resin is a product of Rohm & Haas Company. Diaion HP20 is a product of Mitsubishi Chemical Company. NMR spectra were taken with tetramethylsilane as the internal or external standard using the Gemini 200 model spectrometer; all δ values are expressed in ppm. Regarding mixed solvents, figures in parentheses are mixing ratios by volume for individual solvents. Percent values for solutions are gram numbers in 100 ml of solution. The symbols in Reference Examples and Examples have the following meanings:

s : singlet
d : doublet
t : triplet
q : quartet
ABq: AB type quartet
dd : double doublet
m : multiplet
bs : broad singlet
J : coupling constant

[0048]
[Examples]
Reference Example 1
7β-tert-butoxycarbonylamino-3-[(E)-2-(5-methylthiazolo[4,5-c]pyridinium-2-yl)thioethenyl]-3-cefem-4-carboxylate iodide
To a mixture of diphenylmethyl 7β-tert-butoxycarbonylamino-3-[(E)-2-(tosyloxy)ethenyl]-3-cefem-4-carboxylate 1-oxide (679 mg), 2-mercaptothiazolo[4,5-c]pyridine (216 mg), and dimethylformamide (DMF, 6 ml), diisopropylamine (209 μl) was added, and this was followed by stirring at 60°C for 1 hour. Ethyl acetate (100 ml) was added; the solution was washed with water and saturated saline, after which it was dried ($MgSO_4$). The solvent was distilled off; the residue was subjected to silica gel chromatography and eluted with ethyl acetate to yield diphenylmethyl 7β-tert-butoxycarbonylamino-3-[(E)-2-(thiazolo[4,5-]pyridin-2-yl)thioethenyl]-3-cefem-4-carboxylate 1-oxide as an oil (216 mg, 32.0%).
NMR ($CDCl_3$): 1.48(9H, s), 3.38(1H, d, J=18.2Hz), 4.24(1H, d, J=18.2Hz), 4.58(1H, d, J=4.8Hz), 5.71-5.89(2H, m), 7.00(1H, s), 7.21-7.52(11H, m), 7.63(1H, d, J=15.8Hz), 7.75(1H, d, J=5.6Hz), 8.49(1H,d,

J=5.6Hz), 9.20(1H, s).

A solution of this oil in DMF (1.5 ml) was cooled to -70°C; phosphorus trichloride (86.5 μl) was added, and this was followed by stirring for 10 minutes; the resulting solution was added to aqueous sodium bicarbonate-ethyl acetate (1:1, 20 ml). The organic layer was collected and washed with water, after which it was dried ($MgSO_4$). The solvent was distilled off; the residue was subjected to silica gel chromatography and eluted with hexane-ethyl acetate (1:1) to yield diphenylmethyl 7β-tert-butoxycarbonylamino-3-[(E)-2-(thiazolo[4,5-]pyridin-2-yl)thioethenyl]-3-cefem-4-carboxylate as an oil (182 mg, 83.9%).
NMR ($CDCl_3$): 1.48(9H, s), 3.69(1H, d, J=17.6Hz), 3.82(1H, d, J=17.6Hz), 5.05(1H,d, J=4.8Hz), 5.29(1H, d, J=9.0Hz), 5.69(1H, dd, J=4.8, 9.0Hz), 7.00(1H,s), 7.20-7.49(12H, m), 7.75(1H, d, J=5.6Hz), 8.48(1H, d, J=5.6Hz), 9.20(1H, s).

This oil was dissolved in acetone (12 ml) and tetrahydrofuran (THF, 4 ml); methyl iodide (372 μl) was added, and this was followed by stirring at room temperature for 18 hours. The solvent was distilled off; ether was added to the residue to yield diphenylmethyl 7β-tert-butoxycarbonylamino-3-[(E)-2-(5-methylthiazolo[4,5-c]pyridinium-2-yl)thioethenyl]-3-cefem-4-carboxylate iodide as a crystal (174 mg, 78.7%).
NMR (DMSO-d_6): 1.43(9H, s), 3.75(1H, d, J=18.0Hz), 4.10(1H, d, J=18.0Hz), 4.44(3H, s), 5.24(1H, d, J=5.0Hz), 5.651H, dd, J=5.0, 8.2Hz), 7.00(1H, s), 7.17-7.49(12H, m), 8.13(1H, d, J=8.2Hz), 8.74(1H, d, J=7.2Hz), 8.80(1H, d, J=7.2Hz), 9.74(1H, s).

[0049] Reference Example 2
Diphenylmethyl 7β-tert-butoxycarbonylamino-3-[(E)-2-(1-methylpyridinium-4-ylthiazol-2-yl)thioethenyl]-3-cefem-4-carboxylate iodide
To a mixture of diphenylmethyl 7β-tert-butoxycarbonylamino-3-[(E)-2-(tosyloxy)ethenyl]-3-cefem-4-carboxylate 1-oxide (1.7 g), 4-(4-pyridyl)-2-mercaptothiazole (582 mg), and dimethylformamide (15 ml), triethylamine (0.42 ml) was added drop by drop under ice cooling conditions. After stirring at room temperature for 3 hours, the solution was added to aqueous sodium bicarbonate and extracted with ethyl acetate. After the extract was washed with water and dried ($MgSO_4$), the solvent was distilled off; the residue was dissolved in dimethylformamide (10 ml). Subsequently, phosphorus trichloride (0.65 ml) was added drop by drop at -40°C, and this was followed by stirring at -40°C for 20 minutes; the solution was added to aqueous sodium bicarbonate. After the solution was extracted with ethyl acetate, washed with water, and dried ($MgSO_4$), the solvent was distilled off; the residue was subjected to silica gel chromatography and eluted with ethyl acetate to yield diphenylmethyl 7β-tert-butoxycarbonylamino-3-[(E)-2-(4-(4-pyridyl)thiazol-2-yl)thioethenyl]-3-cefem-4-carboxylate as a crystal (807 mg, 47%).
NMR ($CDCl_3$): 1.48(9H, s), 3.68(1H, d, J=17.2Hz), 3.72(1H, d, J=17.2Hz), 5.04(1H, d, J=4.8Hz), 5.27(1H, d, J=9.2Hz), 5.68(1H, dd, J=4.8, 9.2Hz), 6.99(1H, s), 7.11(1H, d, J=16Hz), 7.30-7.47(11H, m), 7.66(1H, s), 7.76(2H, d, J=6.2Hz), 8.69(2H, d, J=6.2Hz).

A mixture of diphenylmethyl 7β-tert-butoxycarbonylamino-3-[(E)-2-(4-(4-pyridyl)thiazol-2-yl)thioethenyl]-3-cefem-4-carboxylate (137 mg), methyl iodide (0.25 ml), and tetrahydrofuran-acetone (1:3, 2 ml) was stirred at room temperature for 16 hours. The solvent was distilled off; isopropyl ether was added to the residue to yield diphenylmethyl 7β-tert-butoxycarbonylamino-3-[(E)-2-(4-(1-methylpyridinium-4-yl)thiazol-2-yl)thioethenyl]-3-cefem-4-carboxylate iodide as a powder at a 100% recovery rate.
NMR (DMSO-d_6): 1.42(9H, s),3.73(1H, d, J=17.6Hz), 4.07(1H, d, J=17.6Hz), 4.32(3H, s), 5.21(1H, d, J=4.8Hz), 5.61(1H, dd, J=4.8, 9.0Hz), 6.95(1H, s), 7.11(1H, d, J=15.8Hz),7.24-7.49(11H, m), 8.11(1H, d, J=9.0Hz), 8.57(2H, d, J=7.0Hz), 8.98(1H,s), 9.00(2H, d, J=7.0Hz).

[0050] Reference Example 3

7β-amino-3-[4-(1-methylpyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate

To a mixture of 4-(4-pyridyl)-2-mercaptothiazol (388 mg) and tetrahydrofuran (10 ml), NaH (containing 60% oil, 80 mg) was added, and this was followed by stirring at room temperature for 20 minutes. Under cooling conditions at -15°C, p-methoxybenzyl 7-phenylacetamide-3-trifluoromethanesulfonyloxy-3-cefem-4-carboxylate (1.06 g) was added, and this was followed by stirring at -15°C for 30 minutes. Water was added; the crystal obtained was collected by filtration and washed with water and cold acetone to yield p-methoxybenzyl 7-phenylacetamide-3-[4-(4-pyridyl)thiazol-2-yl]thio-3-cefem-4-carboxylate (1.10 g, 87.3%).

NMR (DMSO-d_6): 3.46-3.69(3H, m), 3.70(3H, s), 3.94(1H, d, J=17.8Hz), 5.23(2H, s), 5.28(1H, d), 5.82(1H, dd, J=5.0, 8.0Hz), 6.84(2H, d, J=8.4Hz), 7.22-7.30(7H, m), 7.89(2H, d, J=6.0Hz), 8.52(1H, s), 8.66(2H, d, J=6.0Hz), 9.27(1H, d,J=8.4Hz).

To a mixture of p-methoxybenzyl 7-phenylacetamide-3-[4-(4-pyridyl)thiazol-2-yl]thio-3-cefem-4-carboxylate (1.0 g) and dimethylformamide (15 ml), methyl iodide (2.0 ml) was added, and this was followed by stirring at room temperature for 2 hours. The solvent was distilled off; ether was added to the residue to yield p-methoxybenzyl 7-phenylacetamide-3-[4-(1-methylpyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate iodide as a crystal (1.2 g, 95%).

To a mixture of phosphorus pentachloride (936 mg) and dichloromethane (6 ml), pyridine (0.364 ml) was added drop by drop under ice cooling conditions, and this was followed by stirring under ice cooling conditions for 1 hour. Subsequently, p-methoxybenzyl 7-phenylacetamide-3-[4-(1-methylpyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate iodide (1.16 g) was added, and this was followed by stirring for 1 hour; the resulting solution was cooled to -30°C and methanol (2.0 ml) was added drop by drop. After stirring at -10°C for 1 hour, ether was added, and the supernatant was removed. The residue was dissolved in dichloromethane (6 ml) and anisole (0.5 ml); trifluoroacetic acid (3 ml) was added under ice cooling conditions; after stirring at room temperature for 1 hour, the solvent was distilled off. To the residue, ether was added; the precipitate was collected by filtration, dissolved in aqueous sodium bicarbonate, subjected to Diaion HP-20 chromatography, eluted with 20% ethanol, concentrated, and lyophilized to yield 7β-amino-3-[4-(1-methylpyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate as a powder (427 mg, 70%).

NMR (D_2O): 3.48(1H, d, J=17.6Hz), 3.87(1H, d, J=17.6Hz), 4.30(3H, s), 4.79(1H, d, J=5.2Hz), 5.16(1H, d, J=5.2Hz), 8.27(2H, d, J=7.0Hz), 8.44(1H, s), 8.69(2H, d, J=7.0Hz).

[0051] Reference Example 4

In the same manner as Reference Example 1, diphenylmethyl 7β-tert-butoxycarbonylamino-3-[(E)-2-(7-methylthiazolo[5,4-b]pyridinium-2-yl)thioethenyl]-3-cefem-4-carboxylate iodide was produced.
NMR (DMSO-d_6): 1.42(9H, s), 3.76(1H, d, J=17.6Hz), 4.11(1H, d, J=17.6Hz), 4.50(3H, s), 5.23(1H, d, J=5.4Hz), 5.65(1H, dd, J=5.4, 8.4Hz), 6.99(1H, s), 7.11-7.46(12H, m), 8.08-8.21(2H, m), 8.96(1H, d, J=7.6Hz), 9.07(1H, d, J=5.8Hz).

[0052] Reference Example 5

In the same manner as Reference Example 3, the following compounds were produced.
7β-amino-3-[4-(1-(2-thiazolylmethyl)pyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate hydrochloride
NMR (D_2O): 3.64(1H, d, J=17.6Hz), 3.93(1H, d, J=17.6Hz), 5.19(1H, d, J=5.0Hz), 5.40(1H, d, J=5.0Hz), 6.15(2H, s), 7.73(1H, d, J=3.2Hz), 7.85(1H, d, J=3.2Hz), 8.41(2H, d, J=7.0Hz), 8.59(1H, s), 8.93(2H, d, J=7.0Hz).

7β-amino-3-(5-methylthiazolo[4,5-c]pyridinium-2-yl)thio-3-cefem-4-carboxylate
NMR (D_2O): 3.58(1H, d, J=17.6Hz), 4.03(1H, d, J=17.6Hz), 4.58(3H, s), 4.88(1H, d, J=5.2Hz), 5.27(1H, d, J=5.2Hz), 8.49(2H, m), 9.26(1H, s).

7β-amino-3-[4-(1-methylpyridinium-3-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate
NMR (D_2O): 3.50(1H, d, J=17.4Hz), 3.88(1H, d, J=17.4Hz), 4.42(3H, s), 4.85(1H, d, J=5.2Hz), 5.18(1H, d, J=5.2Hz), 8.05(1H, dd, 6.2, 8.0Hz), 8.15(1H, s), 8.71(1H, d, J=6.2Hz), 8.81(1H, d, J=8.9Hz), 9.21(1H, s).

7β-amino-3-[4-(1-methylpyridinium-2-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate
NMR (DMSO-D_6): 3.50(1H, d, J=17.6Hz), 3.84(1H, d, J=17.6Hz), 4.40(3H, s), 4.66(1H, d, J=5.4Hz), 4.99(1H, d, J=5.4Hz), 8.15(1H, m), 8.36(1H, m),8.51(1H, s), 8.62(1H, m), 9.08(1H, m).

7β-amino-3-[5-methyl-4-(1-methylpyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate
NMR (D_2O): 2.61(3H, s), 3.43(1H, d, J=17.4Hz), 3.80(1H, d, J=17.4Hz), 4.30(3H, s), 4.78(1H, d, J=5.2Hz), 5.12(1H, d, J=5.2Hz), 8.14(1H, d, J=6.4Hz), 8.69(1H, d, J=6.4Hz).

[0053] Reference Example 6

3-(4-pyridyl)thiophen
A mixture of 4-pyridineboric acid (1.23 g), 3-bromothiophen (1.63 g), tetrakis(triphenylphosphine) palladium (0) (0.58 g), a 2M aqueous solution of sodium carbonate (8 ml), toluene (20 ml), and ethanol (5 ml) was refluxed under heating in a nitrogen stream for 5 hours. The solution was extracted with ethyl acetate; the extract was washed with water and dried ($MgSO_4$). The solvent was distilled off; the residue was subjected to silica gel chromatography and eluted with hexane-ethyl acetate (2:1) to yield the title compound (0.8 g, 49.7%).
NMR ($CDCl_3$): 7.45(2H, d, J=2.2Hz), 7.49(2H, d, J=6.2Hz), 7.66(1H, t, J=2.2Hz), 8.62(2H, d, J=6.2Hz).

Reference Example 7

2-(2,4-dinitrophenylthio)-4-(4-pyridyl)thiophen

To a mixture of 3-(4-pyridyl)thiophen (0.8 g), 2,4-dinitrophenylsulphenyl chloride (1.29 g), and nitroethane (15 ml), aluminum chloride (1.33 g) was added, and this was followed by stirring at room temperature for 2 hours. H_2O was added; the solution was neutralized with an aqueous solution of sodium hydrogen carbonate; the insoluble matter was filtered off; the filtrate was extracted with ethyl acetate. The extract was washed with water and dried ($MgSO_4$); the solvent was distilled off. The residue was subjected to silica gel chromatography and eluted with hexane-ethyl acetate (1:1) to yield the title compound (0.85 g, 47.8%).

NMR ($CDCl_3$): 7.25(1H, d, J=9.2Hz), 7.51(2H, d, J=6.2Hz), 7.77(1H, d, J=1.6Hz), 8.02(1H, d, J=1.6Hz), 8.26(1H, dd, J=2.6, 9.2Hz), 8.70(2H, d, J=6.2Hz), 9.13(1H, d, J=2.6Hz).

[0054] Reference Example 8

7β-amino-3-[4-(1-methylpyridinium-4-yl)thiophene-2-yl]thio-3-cefem-4-carboxylate

A mixture of 2-(2,4-dinitrophenylthio)-4-(4-pyridyl)thiophen (0.72 g), potassium hydroxide (0.16 g), and methanol (15 ml) was refluxed under heating for 30 minutes, after which the solvent was distilled off to yield potassium 4-(4-pyridyl)thiophene-2-thiolate as a powder, which was collected by filtration and washed with ether. This product was reacted with p-methoxybenzyl 7-phenylacetamide-3-trifluoro-methanesulfonyloxy-3-cefem-4-carboxylate using the method described in Reference Example 3, and further treated in the same manner as Reference Example 3 to yield the title compound.

NMR (D_2O): 3.08(1H, d, J=17.2Hz), 3.41(1H, d, J=17.2Hz), 4.25(1H, s), 4.63(1H, d, J=6.0Hz), 4.85(1H, d, J=6.0Hz), 7.59(1H, s), 7.99(2H, d, J=6.4Hz), 8.27(1H, s), 8.58(2H, d, J=6.4Hz).

Reference Example 9

7β-amino-3-[4-(1-methylpyridinium-3-yl)thiophene-2-yl]thio-3-cefem-4-carboxylate

Using the same method as in Reference Examples 6, 7, and 8, the title compound was obtained.

NMR (D_2O): 3.29(1H, d, J=17.6Hz), 3.53(1H, d, J=17.6Hz), 4.36(3H, s), 4.65(1H, d, J=4.0Hz), 4.98(1H, d, J=4.0Hz), 7.61(1H, d, J=1.4Hz), 8.00(1H, m), 8.02(1H, d,J=1.4Hz), 8.58(2H, m), 9.01(1H, s).

[0055] Reference Example 10

5-acetyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine

To 2-(2-thienyl)ethylamine (26.0 g), acetic anhydride (42.0 ml) was added drop by drop at -15°C. After stirring at -15°C for 30 minutes and at room temperature for 30 minutes, the solvent was distilled off. The residue was dissolved in toluene (300 ml); p-formaldehyde (7.36 g) and p-toluenesulfonic acid hydrate (1.94 g) were added; with a Dean-Stark apparatus attached, the solution was refluxed under heating for 40 minutes. After the solution was sequentially washed with an aqueous solution of sodium hydrogen carbonate and water, it was dried ($MgSO_4$); the solvent was distilled off. The residue was subjected to silica gel chromatography and extracted with hexane-acetone (2:1) to yield the title compound (24.0 g, 65%).

NMR ($CDCl_3$): 2.18(1.5H, s), 2.20(1.5H, s), 2.52(3H, s), 2.87-2.99(2H, m), 3.76(1H, t, J=5.8Hz), 3.92(1H, t, J=5.8Hz), 4.55(1H, s), 4.67(1H, s), 7.40(1H, s).

Reference Example 11

5-acetyl-4,5,6,7-tetrahydro-2-(2,4-dinitrophenylthio)thieno[3,2-c]pyridine

To a mixture of 5-acetyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (23.8 g), 2,4-dinitrophenylsulphenyl chloride (32.3 g) and nitroethane (240 ml), aluminum chloride (21.0 g) was added gradually under ice

cooling conditions. After stirring under ice cooling conditions for 30 minutes and at room temperature for 1 hour, the solution was added to ice water and extracted with ethyl acetate. After the extract was washed with water and dried ($MgSO_4$), the solvent was distilled off to yield the title compound as a crystal, which was collected by filtration and washed with isopropyl ether (47.0 g, 94%).
NMR ($CDCl_3$): 2.21(1.5H, s), 2.24(1.5H, s), 2.92-3.00(2H, m), 3.83(1H, t, J=5.8Hz), 4.60(1H, s), 4.73(1H, s), 7.15-7.29(2H, m), 8.22-8.29(1H, m), 9.10(0.5H, s), 9.11(0.5H, s).

[0056] Reference Example 12
4,5,6,7-tetrahydro-2-(2,4-dinitrophenylthio)thieno[3,2-c]pyridin
A mixture of 5-acetyl-4,5,6,7-tetrahydro-2-(2,4-dinitrophenylthio)thieno[3,2-c]pyridine (12.3 g), 6N HCl (50 ml), dimethoxyethane (50 ml), and ethanol (15 ml) was refluxed under heating for 7 hours. The solvent was distilled off; the crystal obtained was collected by filtration and washed with acetone. This crystal was added to an aqueous solution of sodium hydrogen carbonate, and this was followed by extraction with acetic acidethyl-tetrahydrofuran (1:1). After the extract was dried ($MgSO_4$), the solvent was distilled off to yield the title compound.
NMR ($CDCl_3$): 2.89(2H, t, J=5.8Hz), 3.22(2H, t, J=5.8Hz), 3.98(2H, s), 7.08(1H, s), 7.27(1H, d, J=9.0Hz), 8.23(1H, dd, J=2.4, 9.0Hz), 9.10(1H, d, J=2.4Hz).

Reference Example 13
2-(2,4-dinitrophenylthio)thieno[3,2-c]pyridine
A mixture of 4,5,6,7-tetrahydro-2-(2,4-dinitrophenylthio)thieno[3,2-c]pyridine (9.33 g), manganese dioxide (50 g), dimethoxyethane (130 ml), and toluene (130 ml) was refluxed under heating for 2 hours. The manganese dioxide was distilled off; the filtrate was concentrated; the crystal obtained was collected by filtration, and washed with ether to yield the title compound (6.62 g, 65%).
NMR ($CDCl_3$): 7.28(1H, d, J=9.0Hz), 7.82-7.86(1H,), 7.88(1H, d, J=1.0Hz), 8.25(1H, dd, J=2.6, 9.0Hz), 8.61(1H, d, J=5.8Hz), 9.15(1H, d, J=2.6Hz), 9.22(1H, d, J=1.0Hz).

[0057] Reference Example 14
Potassium thieno[3,2-c]pyridine-2-thiolate
To a solution of potassium hydroxide (317 mg) in methanol (25 ml), 2-(2,4-dinitrophenylthio)thieno [3,2-c]pyridine (1.33 g) was added, and this was followed by refluxing under heating for 0.5 hours. The solvent was distilled off; the crystal obtained was collected by filtration, and washed with ether to yield the title compound at a 100% recovery rate.
NMR (CD_3OD): 6.85(1H, s), 7.50(1H, d, J=5.0Hz), 7.97(1H, d, J=5.0Hz), 8.45(1H, s).

Reference Example 15
2-(2,4-dinitrophenylthio)thieno[2,3-c]pyridine
Using the method described in Reference Examples 10, 11, 12, and 13, the title compound was produced from 2-(3-thienyl)ethylamine.
NMR ($CDCl_3$): 7.27(1H, d, J=9.0Hz), 7.78(1H, d, J=5.6Hz), 7.80(1H, s), 8.25(1H, dd, J=2.2, 9.0Hz), 8.64(1H, d, J=5.6Hz), 9.15(1H, d, J=2.6Hz), 9.21(1H, s).

[0058] Reference Example 16
Potassium thieno[2,3-c]pyridine-2-thiolate
In the same manner as Reference Example 14, the title compound was produced from 2-(2,4-dinitrophenyl-thio)thieno[2,3-c]pyridine.

NMR (DMSO-d_6): 6.33(1H, s), 6.98(1H, d, J=5.6Hz), 7.93(1H, d, J=5.6Hz), 8.32(1H, s).

Reference Example 17

7β-amino-3-(5-methylthieno[3,2-c]pyridinium-2-yl)thio-3-cefem-4-carboxylate

Using potassium thieno[3,2-c]pyridine-2-thiolate as obtained in Reference Example 14, and using the same method as Reference Example 3, the title compound was obtained.

NMR (DMSO-d_6): 3.20(1H, d, J=17.0Hz), 3.70(1H, d, J=17.0Hz), 4.37(3H, s), 4.65(1H, d, J=5.2Hz), 4.96(1H, d, J=5.2Hz), 7.78(1H, s), 8.62(2H, s), 9.41(1H, s).

Reference Example 18

7β-amino-3-(6-methylthieno[2,3-c]pyridinium-2-yl)thio-3-cefem-4-carboxylate

Using potassium thieno[2,3-c]pyridine-2-thiolate as obtained in Reference Example 16, and using the same method as Reference Example 3, the title compound was obtained.

NMR (DMSO-d_6): 3.25(1H, d, J=17.0Hz), 3.81(1H, d, J=17.0Hz), 4.31(3H, s), 4.69(1H, d, J=5.2Hz), 5.02(1H, d, J=5.2Hz), 7.59(1H, s), 8.11(2H, d, J=6.0Hz), 8.57(1H, d, J=6.0Hz), 9.52(1H, s).

[0059] Reference Example 19

7β-amino-3-[(E)-2-(5-methylthieno[3,2-c]pyridinium-2-yl)thioethenyl]-3-cefem-4-carboxylate ditrifluoroacetate

Potassium thieno[3,2-c]pyridine-2-thiolate (1.17 g) was added little by little to a 0°C cooled solution of diphenylmethyl 7β-tert-butoxycarbonylamino-3-[(E)-2-(tosyloxy)ethenyl]-3-cefem-4-carboxylate 1-oxide (2.46 g) in dimethylformamide (20 ml). After stirring at 0°C for 30 minutes, the solution was diluted with ethyl acetate, washed with water, and dried ($MgSO_4$), after which the solvent was distilled off. The residue was dissolved in dimethylformamide (18 ml); phosphorus trichloride (0.96 ml) was added drop by drop under cooling at -40°C. The solution was stirred at -40°C for 15 minutes, added to ice water, and extracted with ethyl acetate. The extract was sequentially washed with an aqueous solution of sodium hydrogen carbonate and water, after which it was dried ($MgSO_4$). The solvent was distilled off; the residue was subjected to silica gel chromatography and eluted with hexane-ethyl acetate (1:1) to yield diphenylmethyl 7β-tert-butoxycarbonylamino-3-[(E)-2-(thieno[3,2-c]pyridin-2-yl)thioethenyl]-3-cefem-4-carboxylate (1.27 g). This product was dissolved in dimethylformamide (8 ml); methyl iodide (2 ml) was added, and this was followed by stirring at room temperature for 3 hours. The solvent was distilled off; isopropyl ether was added to the residue, and this was followed by vigorous stirring, after which the isopropyl ether was removed. The residue was dissolved in dichloromethane (10 ml) and anisole (2 ml); trifluoroacetic acid (10 ml) was added under ice cooling conditions, and this was followed by stirring at room temperature for 2 hours, after which the solvent was distilled off; ether was added; the precipitate was collected by filtration to yield the title compound.

NMR (DMSO-d_6): 3.66(1H, d, J=18.0Hz), 3.97(1H, d, J=18.0Hz), 4.41(3H, s), 4.93(1H, d, J=5.2Hz), 5.11(1H, d, J=5.2Hz), 7.16(2H, s), 8.03(1H, s), 8.71(2H, s), 9.47(1H, s).

[0060] Reference Example 20

7β-amino-3-[4-(1-carbamoylmethylpyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate

To a solution of phosphorus pentachloride (1.25 g) in dichloromethane (10 ml), pyridine (0.45 ml) was added under ice cooling conditions. After stirring under ice cooling conditions for 30 minutes, p-methoxybenzyl 7β-phenylacetamide-3-[4-(4-pyridyl)thiazol-2-yl]thio-3-cefem-4-carboxylate as obtained in Reference Example 3 (1.4 g) was added. After stirring under ice cooling conditions for 1 hour, methanol (2 ml) was added drop by drop under ice cooling conditions at -30°C. After stirring at 0°C for 30 minutes,

ether (50 ml) was added and the supernatant was removed. To the residue, an aqueous solution of sodium hydrogen carbonate was added, and this was followed by extraction with ethyl acetate. After the extract was washed with water and dried ($MgSO_4$), the solvent was distilled off; the residue was dissolved in tetrahydrofuran (10 ml). Di-tert-butyl bicarbonate (0.83 g) was added, and this was followed by stirring at room temperature for 2 hours, after which acetic acidethyl was added; after the solution was washed with water and dried ($MgSO_4$), the solvent was distilled off. The residue was subjected to silica gel chromatography and eluted with hexane-acetone (1:1) to yiled p-methoxybenzyl 7β-tert-butoxycarbonylamino-3-[4-(4-pyridyl)thiazol-2-yl]thio-3-cefem-4-carboxylate. This product was dissolved in dimethylformamide (6 ml); acetamide iodide (1.8 g) was added, and this was followed by stirring at room temperature for 45 hours; ether was added; the precipitate was collected by filtration to yield p-methoxybenzyl 7β-tert-butoxycarbonylamino-3-[4-(1-carbamoylmethylpyridinium-4-yl)thiazol-2-yl] thio-3-cefem-4-carboxylate iodide (0.6 g). This product was dissolved in dichloromethane (5 ml) and anisole (0.5 ml); trifluoroacetic acid (5 ml) was added under ice cooling conditions, and this was followed by stirring at room temperature for 40 minutes. Ether was added; the precipitated powder was collected by filtration to yield the title compound (0.4 g, 95.2%).
NMR (DMSO-d_6): 3.75(1H, d, J=16.6Hz), 3.99(1H, d, J=16.6Hz), 5.24(1H, d, J=6.0Hz), 5.36(1H, d, J=6.0Hz), 5.39(2H, s), 7.73(1H, s), 8.08(1H, s), 8.61(2H, d, J=6.0Hz), 8.98(2H, d, J=6.0Hz), 9.11(1H, s).

[0061] Example 1
7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-methoximinoacetamide]-3-[(E)-2-(5-methylthiazolo[4,5-c]pyridinium-2-yl)thioethenyl]-3-cefem-4-carboxylate
To a mixture of diphenylmethyl 7β-tert-butoxycarbonylamino-3-[(E)-2-(5-methylthiazolo[4,5-c]pyridinium-2-yl)thioethenyl]-3-cefem-4-carboxylate iodide (86 mg), dichloromethane (0.7 ml), and anisole (100 μ), trifluoroacetic acid (0.7 ml) was added, and this was followed by stirring at room temperature for 1 hour. The solvent was distilled off; saturated aqueous sodium bicarbonate (1.0 ml) and THF (1.0 ml) were added to the residue; while stirring under ice cooling conditions, 2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-methoximinoatylchloride hydrochloride (55 mg) was added. After 10 minutes, the THF was distilled off; the residue was subjected to Diaion HP-20 column chromatography, eluted with 20% ethanol, concentrated, and lyophilized to yield the title compound (25 mg, 39.6%).
IR (KBr) cm^{-1}: 3400, 1770, 1670, 1603.
NMR (DMSO-d_6): 3.54(1H, d, J=17.0Hz), 3.68(1H, d, J=17.0Hz), 3.93(3H, s), 4.41(3H, s), 5.13(1H, d, J=5.0Hz), 5.68(1H, dd, J=5.0, 8.2Hz), 6.65(1H, d, J=15.2Hz), 7.68(1H, d, J=15.2Hz), 8.16(2H, s), 8.71(1H, d, J=6.6Hz), 8.76(1H, d, J=6.6Hz), 9.58(1H,d, J=8.2Hz), 9.70(1H, s).

Example 2
In the same manner as Example 1, the following compound was produced.
7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoximinoacetamide]-3-[(E)-2-(5-methylthiazolo[4,5-c]pyridinium-2-yl)thioethenyl]-3-cefem-4-carboxylate
IR (KBr) cm^{-1}: 3425, 1770, 1670, 1610.
NMR (DMSO-d_6): 3.55(1H, d, J=16.8Hz), 3.67(1H, d, J=16.8Hz), 4.41(3H, s), 5.14(1H, d, J=5.0Hz), 5.67(1H, dd, J=5.0, 7.8Hz), 5.81(2H, d, J=54.2Hz), 6.64(1H, d, J=15.4Hz), 7.70(1H, d, J=15.4Hz), 8.23(2H, s), 8.70(1H, d, J=6.6Hz), 8.76(1H, d, J=6.6Hz), 9.68(1H, s), 9.76(1H, d, J=7.8Hz).

[0062] Example 3
In the same manner as Example 1, the following compound was produced.
7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-ethoximinoacetamide]-3-[(E)-2-(5-methylthiazolo[4,5-

c]pyridinium-2-yl)thioethenyl]-3-cefem-4-carboxylate
IR (KBr) cm^{-1}: 3400, 1762, 1670, 1605.
NMR (DMSO-d_6): 1.29(3H, t, 7.0Hz), 3.58(1H, d, 16.8Hz), 3.75(1H, d, J=16.8Hz), 4.21(2H, q, J=7.0Hz), 4.43(3H, s), 5.17(1H, d, J=5.2Hz), 7.75(1H, dd, J=5.2, 8.0Hz), 6.77(1H, d, J=15.4Hz), 7.64(1H, d, J=15.4Hz), 8.17(2H, s), 8.721H, d, J=6.6Hz), 8.78(1H, d, J=6.6Hz), 9.58(1H, d, J=8.0Hz), 9.71(1H, s).

Example 4
In the same manner as Example 1, the following compound was produced.
7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-isopropoximinoacetamide]-3-[(E)-2-(5-methylthiazolo[4,5-c]pyridinium-2-yl)thioethenyl]-3-cefem-4-carboxylate
IR (KBr) cm^{-1}: 3400, 1762, 1670, 1602.
NMR (DMSO-d_6): 1.19-1.30(6H, m), 3.55(1H, d, J=16.8Hz), 3.70(1H, d, J=16.8Hz), 4.41(1H, m), 4.42(3H, s), 5.15(1H, d, J=5.2Hz), 5.70(1H, dd, J=5.2, 8.4Hz), 6.69(1H, d, J=15.4Hz), 7.68(1H, d, J=15.4Hz), 8.17(2H, s), 8.71(1H, d, 6.8Hz), 8.77(1H, d, J=6.8Hz), 9.53(1H, d, J=8.4Hz), 9.70(1H, s).

[0063] Example 5
In the same manner as Example 1, the following compound was produced.
7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-cyclopentyloximinoacetamide]-3-[(E)-2-(5-methylthiazolo[4,5-c]pyridinium-2-yl)thioethenyl]-3-cefem-4-carboxylate
IR (KBr) cm^{-1}: 3400, 1762, 1662, 1602.
NMR (DMSO-d_6): 1.24-1.92(8H, m), 3.53(1H, d, J=16.8Hz), 3.66(1H, d, J=16.8Hz), 4.41(3H, s), 4.74(1H, m), 5.13(1H, d, J=5.0Hz), 5.64(1H, dd, J=6.0, 8.4Hz), 6.95(1H, d, J=15.0), 7.69(1H, d, J=15.0Hz), 8.15(2H, s), 8.70(1H, d, J=6.6Hz), 8.76(1H, d, J=6.6Hz), 9.52(1H, d, J=8.4Hz), 9.68(1H, s).

Example 6
7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-methoximinoacetamide]-3-[(E)-2-(4-(1-methylpyridinium-4-yl)thiazol-2-yl)thioethenyl-3-cefem-4-carboxylate
To a mixture of diphenylmethyl 7β-tert-butoxycarbonylamino-3-[(E)-2-(4-(1-methylpyridinium-4-yl)thiazol-2-yl)thioethenyl]-3-cefem-4-carboxylate iodide (130 mg), anisole (0.25 ml), and dichloromethane (1.5 ml), trifluoroacetic acid (1.5 ml) was added under ice cooling conditions, and this was followed by stirring at room temperature for 1 hour. Ether was added; the precipitate was collected by filtration and dissolved in tetrahydrofuran-water (1:1, 2 ml); while the solution was kept at pH 9 with aqueous sodium bicarbonate, 2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-methoximinoatylchloride hydrochloride (82 mg) was added. After stirring for 30 minutes, the tetrahydrofuran was distilled off; the residue was subjected to Diaion HP-20 chromatography, eluted with 20% ethanol, concentrated, and lyophilized to yield the title compound (9 mg, 9%).
IR (KBr): 1765, 1640, 1605.
NMR (DMSO-d_6): 3.52(1H, d, J=18.4Hz), 3.62(1H, d, J=18.4Hz), 3.93(3H, s), 4.30(3H, s), 5.09(1H, d, J=5.2Hz), 5.65(1H, dd, J=5.2, 8.4Hz), 6.53(1H, d, J=15.4Hz), 7.57(1H, d, J=15.4Hz), 8.14(2H, s), 8.56(2H, d, J=6.8Hz), 8.92(1H, s), 8.97(2H, d, J=6.8Hz), 9.56(1H, d, 8.4Hz).

[0064] Example 7
In the same manner as Example 6, the following compound was produced.
7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoximinoacetamide]-3-[(E)-2-(4-(1-methylpyridinium-4-yl)thiazol-2-yl)thioethenyl-3-cefem-4-carboxylate
IR (KBr): 1765, 1640, 1600.

NMR (DMSO-d_6): 3.53(1H, d, J=17Hz), 3.63(1H, d, J=17.0Hz), 4.31(3H, s), 5.11(1H, d, J=4.8Hz), 5.67(1H, dd, J=4.8, 8.4Hz), 5.80(2H, d, J=54.0Hz), 6.53(1H, d, J=15.2Hz), 7.57(1H, d, J=15.2Hz), 8.23(2H, bs), 8.56(2H, d, J=6.4Hz), 8.93(1H, s), 8.98(2H, d, J=6.4Hz), 9.76(1H, d, J=8.4Hz).

Example 8

In the same manner as Example 6, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-ethoximinoacetamide]-3-[(E)-2-(4-(1-methylpyridinium-4-yl) thiazol-2-yl)thioethenyl-3-cefem-4-carboxylate

IR (KBr): 1765, 1640, 1600.

NMR (DMSO-d_6): 1.27(3H, t, J=7.0Hz), 3.53(1H, d, J=18.0Hz), 3.64(1H, d, J=18.0Hz), 4.19(2H, q, J=7.0Hz), 4.31(3H, s), 5.10(1H, d, J=5.0Hz), 5.66(1H, dd, J=5.0, 8.4Hz), 6.53(1H, d, J=15.2Hz), 7.57(1H, d, J=15.2Hz), 8.16(2H, bs), 8.57(2H, d, J=7.0Hz), 8.93(1H, s), 8.98(2H, d, J=7.0Hz), 9.55(1H, d, J=8.4Hz).

[0065] Example 9

In the same manner as Example 6, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-isopropoximinoacetamide]-3-[(E)-2-(4-(1-methylpyridinium-4-yl)thiazol-2-yl)thioethenyl-3-cefem-4-carboxylate

IR (KBr): 1760, 1635, 1600.

NMR (DMSO-d_6): 1.26(3H, d, J=6.0Hz), 1.28(3H, d, J=6.0Hz), 3.52(1H, d, J=17.2Hz), 3.64(1H, d, J=17.2Hz); 4.31(3H, s), 4.31-4.48(1H, m), 5.10(1H, d, J=5.0Hz), 5.66(1H, dd, J=5.0, 8.4Hz), 6.53(1H, d, J=15.4Hz), 7.56(1H, d, J=15.4Hz), 8.16(2H, s), 8.52(2H, d, J=6.2Hz), 8.92(1H, s), 8.97(2H, d, J=6.2Hz), 9.52(1H, d, J=8.4Hz).

Example 10

In the same manner as Example 6, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-cyclopentyloximinoacetamide]-3-[(E)-2-(4-(1-methylpyridinium-4-yl)thiazol-2-yl)thioethenyl-3-cefem-4-carboxylate

IR (KBr): 1765, 1635, 1605.

NMR (DMSO-d_6): 1.42-2.00(8H, m), 3.52(1H, d, J=17.6Hz), 3.62(1H, d, J=17.6Hz), 4.31(3H, s), 4.70-4.77(1H, m), 5.10(1H, d, J=4.8Hz), 5.64(1H, dd, J=4.8, 8.2Hz), 6.53(1H, d, J=15.2Hz), 7.57(1H, d, 15.2Hz), 8.15(2H, bs), 8.56(2H, d, J=6.6Hz), 8.92(1H, s), 8.98(2H, d, J=6.6Hz), 9.50(1H, d, J=8.2Hz).

[0066] Example 11

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-isopropoximinoacetamide]-3-[4-(1-methylpyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate

To a solution of 7-amino-3-[4-(1-methylpyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate (81 mg) in water-tetrahydrofuran (1:2, 3 ml) being adjusted to pH 8 with aqueous sodium bicarbonate, 2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-isopropoximinoatyl chloride hydrochloride (86 mg) was added little by little. After 15 minutes, the tetrahydrofuran was distilled off; the residue was subjected to Diaion HP-20 chromatography, eluted with 20% and 25% ethanol, concentrated, and lyophilized to yield the title compound (47 mg, 40.5%).

IR (KBr): 1775, 1640, 1610.

NMR (DMSO-d_6): 1.23(3H, d, J=6.4Hz), 1.27(3H, d, J=6.4Hz), 3.32(1H, d, J=17.2Hz), 3.90(1H, d, J=17.2Hz), 4.32(3H, s), 4.39(1H, m), 5.19(1H, d, J=5.2Hz), 5.72(1H, dd, J=5.2, 8.4Hz), 8.17(2H, s), 8.46(2H, d, J=6.6Hz), 8.89(1H, s), 8.97(2H, d, J=6.6Hz), 9.61(1H,d, J=8.4Hz).

Example 12

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoximinoacetamide]-3-[4-(1-methylpyridinium-4-yl) thiazol-2-yl]thio-3-cefem-4-carboxylate

IR (KBr): 1775, 1640, 1610.

NMR (DMSO-d_6): 3.34(1H, d, J=16.8Hz), 3.89(1H, d, J=16.8Hz), 4.30(3H, s), 5.19(1H, d, J=5.0Hz), 5.74(1H, dd, J=5.0, 8.4Hz), 5.79(2H, d, J=54.6Hz), 8.22(2H, d, J=6.8Hz), 8.49(2H, d, J=6.8Hz), 8.88(1H, s), 8.95(2H, d, J=6.8Hz), 9.84(1H, d, J=8.4Hz).

[0067] Example 13

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-ethoximinoacetamide]-3-[4-(1-methylpyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate

IR (KBr): 1775, 1640, 1615.

NMR (DMSO-d_6): 1.25(3H, t, J=7.0Hz), 3.34(1H, d, J=17.2Hz), 3.89(1H, d, J=17.2Hz), 4.18(2H, q, J=7.0Hz), 4.30(3H, s), 5.18(1H, d, J=5.2Hz), 5.73(1H, dd, J=5.2, 8.4Hz), 8.13(2H, s), 8.49(2H, d, J=6.6Hz), 8.88(1H, s), 8.95(2H, d, J=6.6Hz), 9.62(1H, d, J=8.4Hz).

Example 14

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-cyclopentyloximinoacetamide]-3-[4-(1-methylpyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate

IR (KBr): 1770, 1640, 1615.

NMR (DMSO-d_6): 1.42-1.98(8H, m), 3.33(1H, d, J=17.6Hz), 3.90(1H, d, J=17.6Hz), 4.30(3H, s), 4.70-4.78(1H, m), 5.18(1H, d, J=5.2Hz), 5.70(1H, dd, J=5.2, 8.2Hz), 8.14(2H, s), 8.49(2H, d, J=6.6Hz), 8.89(1H, s), 8.95(2H, d, J=6.6Hz), 9.75(1H, d, J=8.2Hz).

[0068] Example 15

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-methoximinoacetamide]-3-[4-(1-methylpyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate

IR (KBr): 1770, 1640, 1610.

NMR (DMSO-d_6): 3.53(1H, d, J=17.5Hz), 3.91(1H, d, J=17.5Hz), 3.92(3H, s), 4.31(3H, s), 5.17(1H, d, J=5.2Hz), 5.74(1H, dd, J=5.2, 8.4Hz), 8.15(2H, s), 8.47(2H, d, J=6.6Hz), 8.89(1H, s), 8.97(2H, d, J=6.6Hz), 9.66(1H, d, J=8.4Hz).

Example 16

In the same manner as Example 1, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-methoximinoacetamide]-3-[(E)-2-(7-methylthiazolo[5,4-b]pyridinium-2-yl)thioethenyl]-3-cefem-4-carboxylate

IR (KBr): 3400, 1770, 1670, 1600.

NMR (DMSO-d_6): 3.58(1H, d, J=17.0Hz), 3.73(1H, d, J=17.0Hz), 3.93(3H, s), 4.50(3H, s), 5.13(1H, d, J=4.8Hz), 5.69(1H, dd, J=4.8, 8.4Hz), 6.66(1H, d, J=15.2Hz), 7.71(1H, d, J=15.2Hz), 8.09-8.17(4H, m), 8.91(1H, d, J=8.2Hz), 9.04(1H, d, J=5.8Hz), 9.58(1H,d, J=8.4Hz).

[0069] Example 17

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-methoximinoacetamide]-3-[4-(1-(2-thiazolylmethyl)pyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate

IR (KBr): 1770, 1670, 1635, 1610.

NMR (DMSO-d_6): 3.34(1H, d, J=16.8Hz), 3.89(1H, d, J=16.8Hz), 3.91(3H, s), 5.16(1H, d, J=5.2Hz), 5.72(1H, dd, J=5.2, 8.4Hz), 6.24(2H, s), 7.86(1H, d, J=3.2Hz), 7.89(2H, d, J=3.2Hz), 8.12(2H, bs), 8.58(2H, d, J=6.8Hz), 8.93(1H, s), 9.16(2H, d, J=6.8Hz), 9.63(1H, d, J=8.4Hz).

Example 18

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoximinoacetamide]-3-[4-(1-(2-thiazolylmethyl)pyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate

IR (KBr): 1770, 1670, 1635, 1610.

NMR (DMSO-d_6): 3.34(1H, d, J=17.0Hz), 3.90(1H, d, J=17.0Hz), 4.30(3H, s), 5.19(1H, d, J=5.2Hz), 5.74(1H, dd, J=5.2, 8.0Hz), 5.78(2H, d, J=55.2Hz), 6.25(2H, s), 7.86(1H, d, J=3.2Hz), 7.88(1H, d, J=3.2Hz), 8.20(2H, s), 8.57(2H, d, J=6.6Hz), 8.92(1H, s), 9.16(2H, d, J=6.6Hz), 9.84(1H, d, J=8.0Hz).

[0070] Example 19

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-methoximinoacetamide]-3-(1-(5-methylthiazolo[4,5-c]pyridinium-2-yl)thio-3-cefem-4-carboxylate

IR (KBr): 1775, 1645, 1610.

NMR (D_2O): 3.61(1H, d, J=18.4Hz), 4.07(1H, d, J=18.4Hz), 4.08(3H, s), 4.52(3H, s), 5.44(1H, d, J=4.8Hz), 5.92(1H, d, J=4.8Hz), 8.48(2H, m), 9.26(1H, s).

Example 20

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoximinoacetamide]-3-(1-(5-methylthiazolo[4,5-c]pyridinium-2-yl)thio-3-cefem-4-carboxylate

IR (KBr): 1775, 1645, 1610.

NMR (D_2O): 3.63(1H, d, J=16.8Hz), 4.09(1H, d, J=16.8Hz), 4.47(3H, s), 5.47(1H, d, J=4.6Hz), 5.87(1H, d, J=53.8Hz), 5.87(1H, d, J=4.6Hz), 8.49(2H, m), 9.27(1H, s).

[0071] Example 21

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-methoximinoacetamide]-3-[4-(1-methylpyridinium-3-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate

IR (KBr): 1770, 1665, 1610.

NMR (DMSO-d_6): 3.31(1H, d, J=16.4Hz), 3.87(1H, d, J=16.4Hz), 3.92(3H, s), 4.42(3H, s), 5.16(1H, d, J=5.2Hz), 5.72(1H, dd, J=5.2, 8.6Hz), 8.12-8.18(3H, m), 8.52(1H, s), 8.92(1H, d, J=6.2Hz), 8.99(1H, d, J=9.2Hz), 9.52(1H, s), 9.64(1H, d, J=8.6Hz).

Example 22

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoximinoacetamide]-3-[4-(1-methylpyridinium-3-yl)

thiazol-2-yl]thio-3-cefem-4-carboxylate
IR (KBr): 1770, 1670, 1620.
NMR (DMSO-d_6): 3.31(1H, d, J=16.8Hz), 3.88(1H, d, J=16.8Hz), 4.42(3H, s), 5.18(1H, d, J=5.0Hz), 5.74(1H, dd, J=5.0, 8.4Hz), 5.79(2H, d, J=55.4Hz), 8.16(1H, dd, J=5.6, 8.4Hz), 8.22(2H, s), 8.51(1H, s), 8.92(1H, d, J=5.6Hz), 8.98(1H, d, J=8.4Hz), 9.52(1H, s), 9.85(1H, d, J=8.4Hz).

[0072] Example 23
In the same manner as Example 11, the following compound was produced.
7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-methoximinoacetamide]-3-[4-(1-methylpyridinium-2-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate
IR (KBr): 1770, 1660, 1610.
NMR (DMSO-d_6): 3.28(1H, d, J=16.0Hz), 3.86(1H, d, J=16.0Hz), 3.92(3H, s), 4.40(3H, s), 5.16(1H, d, J=5.0Hz), 5.72(1H,dd, J=5.0, 8.2Hz), 8.11(1H, m), 8.16(2H, s), 8.53(1H, s), 8.64(1H, m), 9.52(1H, d, J=5.2Hz), 9.66(1H, d, J=8.4Hz).

Example 24
In the same manner as Example 11, the following compound was produced.
7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoximinoacetamide]-3-[4-(1-methylpyridinium-2-yl) thiazol-2-yl]thio-3-cefem-4-carboxylate
IR (KBr): 1775, 1660, 1615.
NMR (DMSO-d_6): 3.30(1H, d, J=17.6Hz), 3.86(1H, d, J=17.6Hz), 4.40(3H, s), 5.18(1H, d, J=5.0Hz), 5.73(1H, dd, J=5.0, 8.4Hz), 8.11(1H, m), 8.25(2H, s), 8.34(1H, d, J=7.8Hz), 8.63(1H, m), 9.11(1H, d, J=3.8Hz), 9.86(1H, d, J=8.4Hz).

[0073] Example 25
In the same manner as Example 11, the following compound was produced.
7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-isopropoximinoacetamide]-3-[4-(1-methylpyridinium-2-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate
IR (KBr): 1770, 1660, 1610.
NMR (DMSO-d_6): 1.22(3H, d, J=4.6Hz), 1.27(3H, d, J=4.6Hz), 3.27(1H, d, J=17.2Hz), 3.88(1H, d, J=17.2Hz), 4.37(1H, m), 4.40(3H, s), 5.18(1H, d, J=5.0Hz), 5.73(1H, dd, J=5.0, 9.0Hz), 8.11(1H, m), 8.17(2H, s), 8.54(1H, s,), 8.63(1H, m), 9.11(1H, d, J=6.0Hz), 9.61(1H, d, J=8.6Hz).

Example 26
In the same manner as Example 11, the following compound was produced.
7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-methoximinoacetamide]-3-[4-(1-methylpyridinium-3-yl)thiophene-2-yl]thio-3-cefem-4-carboxylate
IR (KBr): 1770, 1660, 1610.
NMR (DMSO-d_6): 3.19(1H, d, J=18.6Hz), 3.41(1H, d, J=18.6Hz), 3.88(3H, s), 4.39(3H, s), 4.99(1H, d, J=5.0Hz), 5.58(1H, dd, J=5.0, 9.0Hz), 7.91(1H, d, J=1.4Hz), 8.14(3H, m), 8.44(1H, d, J=1.4Hz), 8.89(2H, d, J=6.2Hz), 9.50(1H, d, J=8.6Hz), 9.53(1H, s).

[0074] Example 27
In the same manner as Example 11, the following compound was produced.
7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoximinoacetamide]-3-[4-(1-methylpyridinium-3-yl) thiophene-2-yl]thio-3-cefem-4-carboxylate

IR (KBr): 1770, 1665, 1610.
NMR (DMSO-d_6): 3.19(1H, d, J=17.0Hz), 3.40(1H, d, J=17.0Hz), 4.39(3H, s), 5.01(1H, d, J=4.6Hz), 5.61(1H, dd, J=4.6, 8.0Hz), 5.75(2H, d, J=55.2Hz), 7.91(1H, d, J=1.4Hz), 8.14(1H,), 8.23(2H, s), 8.43(1H, d, J=1.4Hz), 8.89(2H, d, J=6.2Hz), 9.53(1H, s), 9.70(1H, d, J=8.0Hz).

Example 28
In the same manner as Example 11, the following compound was produced.
7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-isopropoximinoacetamide]-3-[4-(1-methylpyridinium-3-yl) thiophene-2-yl]thio-3-cefem-4-carboxylate
IR (KBr): 1770, 1660, 1615.
NMR (DMSO-d_6): 1.19(3H, d, J=3.2Hz), 1.22(3H, d, J=3.2Hz), 3.18(1H, d, J=17.2Hz), 3.49(1H, d, J=17.2Hz), 4.36(1H, m), 4.39(3H, s), 5.01(1H, d, J=4.8Hz), 5.61(1H, dd, J=4.8, 8.6Hz), 7.91(1H, d, J=1.4Hz), 8.16(3H, m), 8.44(1H, d, J=1.4Hz), 8.89(2H, d, J=7.0Hz), 9.52(1H, s).

[0075] Example 29
In the same manner as Example 11, the following compound was produced.
7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-isopropoximinoacetamide]-3-[4-(1-methylpyridinium-3-yl) thiazol-2-yl]thio-3-cefem-4-carboxylate
IR (KBr): 1770, 1670, 1610.
NMR (DMSO-d_6): 1.23(3H, d, J=6.0Hz), 1.26(3H, d, J=6.0Hz), 3.31(1H, d, J=16.8Hz), 3.88(1H, d, J=16.8Hz), 4.33-4.45(1H, m), 4.42(3H, s), 5.18(1H, d, J=5.2Hz), 5.73(1H, dd, J=5.2, 8.6Hz), 8.13-8.20(3H, m), 8.52(1H, s), 8.92(1H, d, J=5.6Hz), 8.98(1H, d, J=8.2Hz), 9.52(1H, s), 9.60(1H, d, J=8.6Hz).

Example 30
In the same manner as Example 11, the following compound was produced.
7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-ethoximinoacetamide]-3-[4-(1-methylpyridinium-3-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate
IR (KBr): 1770, 1670, 1615.
NMR (DMSO-d_6): 1.25(3H, t, J=7.0Hz), 3.31(1H, d, J=17.2Hz), 3.87(1H, d, J=17.2Hz), 4.18(2H, q, J=7.0Hz), 4.42(3H, s), 5.17(1H, d, J=5.0Hz), 5.73(1H, dd, J=5.0, 8.4Hz), 8.12-8.19(3H, m), 8.51(1H, s), 8.91(1H, d, J=6.2Hz), 8.97(1H, d, J=8.6Hz), 9.51(1H, s), 9.63(1H, d, J=8.4Hz).

[0076] Example 31
In the same manner as Example 11, the following compound was produced.
7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-methoximinoacetamide]-3-(5-methylthieno[3,2-c]pyridinium-2-yl)thio-3-cefem-4-carboxylate
IR (KBr): 1770, 1665, 1610.
NMR (DMSO-d_6): 3.23(1H, d, J=17.0Hz), 3.70(1H, d, J=17.0Hz), 3.89(3H, s), 4.48(3H, s), 5.10(1H, d, J=5.2Hz), 5.68(1H, dd, J=5.2, 8.2Hz), 7.82(1H, s), 8.14(2H, bs), 8.63(2H, s), 9.42(1H, s), 9.60(1H, d, J=8.2Hz).

Example 32
In the same manner as Example 11, the following compound was produced.
7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoximinoacetamide]-3-(5-methylthieno[3,2-c]pyridinium-2-yl)thio-3-cefem-4-carboxylate
IR (KBr): 1770, 1670, 1610.

NMR (DMSO-d_6): 3.22(1H, d, J=16.6Hz), 3.71(1H, d, J=16.6Hz), 4.38(3H, s), 5.13(1H, d, J=5.0Hz), 7068(1H, dd, J=5.0, 8.2Hz), 5.77(2H, d, J=55.2Hz), 7.82(1H, s), 8.23(2H, bs), 8.63(2H, s), 9.43(1H, s), 9.80(1H, d, J=8.2Hz).

[0077] Example 33

In the same manner as Example 1, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoximinoacetamide]-3-[(E)-2-(5-methylthieno[3,2-c]pyridinium-2-yl)thioethenyl]-3-cefem-4-carboxylate

IR (KBr): 1760, 1670, 1600.

NMR (DMSO-d_6): 3.49(1H, d, J=17.2Hz), 3.63(1H, d, J=17.2Hz), 4.83(3H, s), 5.10(1H, d, J=5.2Hz), 5.65(1H, dd, J=5.2, 8.4Hz), 5.80(2H, d, J=55.0Hz), 6.51(1H, d, J=15.2Hz), 7.50(1H, d, J=15.2Hz), 7.81(1H, s), 8.23(2H, bs), 8.64(2H, s), 9.40(1H, s), 9.75(1H, d, J=8.4Hz).

Example 34

In the same manner as Example 1, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoximinoacetamide]-3-[(E)-2-(7-methylthiazolo[5,4-b]pyridinium-2-yl)thioethenyl]-3-cefem-4-carboxylate

IR (KBr): 1760, 1670, 1600.

NMR (DMSO-d_6): 3.57(1H, d, J=16.0Hz), 3.70(1H, d, J=16.0Hz), 4.51(3H, s), 5.15(1H, d, J=4.8Hz), 5.69(1H, dd, J=4.8, 8.0Hz), 5.81(2H, d, J=55.8Hz), 6.62(1H, d, J=14.8Hz), 7.73(1H, d, J=14.8Hz), 8.13(1H, dd, J=6.0, 8.4Hz), 8.24(2H, s), 8.92(1H, d, J=8.4Hz), 9.04(1H, d, J=6.0Hz), 9.78(1H, d, J=8.0Hz).

[0078] Example 35

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-isopropoximinoacetamide]-3-(5-methylthieno[3,2-c]pyridinium-2-yl)thio-3-cefem-4-carboxylate

IR (KBr): 1770, 1665, 1610.

NMR (DMSO-d_6): 1.21(3H, d, J=6.2Hz), 1.23(3H, d, J=6.2Hz), 3.23(1H, d, J=16.8Hz), 3.70(1H, d, J=16.8Hz), 4.30-4.44(1H, m), 4.38(3H, s), 5.12(1H, d, J=4.8Hz), 5.71(1H, dd, J=4.8, 8.4Hz), 7.84(1H, s), 8.16(2H, bs), 8.64(2H, s), 9.42(1H, s), 9.55(1H, d, J=8.4Hz).

Example 36

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoximinoacetamide]-3-(6-methylthieno[2,3-c]pyridinium-2-yl)thio-3-cefem-4-carboxylate

IR (KBr): 1770, 1670, 1615.

NMR (DMSO-d_6): 3.29(1H, d, J=17.0Hz), 3.83(1H, d, J=17.0Hz), 4.31(3H, s), 5.19(1H, d, J=5.0Hz), 5.74(1H, dd, J=5.0,8.4Hz), 5.79(2H, d, J=54.6Hz), 7.64(1H, s), 8.14(1H, d, J=6.6Hz), 8.22(2H, bs), 8.58(1H, d, J=6.6Hz), 9.51(1H, s), 9.85(1H, d, J=8.4Hz).

[0079] Example 37

In the same manner as Example 1, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-isopropoximinoacetamide]-3-[(E)-2-(5-methylthiazolo[3,2-c]pyridinium-2-yl)thioethenyl]-3-cefem-4-carboxylate

IR (KBr): 1760, 1670, 1600.

NMR (DMSO-d_6): 1.26(3H, d, J=6.2Hz), 1.28(3H, d, J=6.2Hz), 3.48(1H, d, J=16.8Hz), 3.64(1H, d,

J=16.8Hz), 4.34-4.46(1H, m), 4.39(3H, s), 5.09(1H, d, J=4.8Hz), 5.65(1H, dd, J=4.8, 8.4Hz), 6.52(1H, d, J=15.2Hz), 7.49(1H, d, J=15.2Hz), 7.81(1H, s), 8.18(2H, bs), 8.64(2H, s), 9.41(1H, s), 9.52(1H, d, J=8.4Hz).

Example 38

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-isopropoximinoacetamide]-3-(6-methylthieno[2,3-c]pyridinium-2-yl)thio-3-cefem-4-carboxylate

IR (KBr): 1770, 1660, 1615.

NMR (DMSO-d_6): 1.23(3H, d, J=6.2Hz), 1.25(3H, d, J=6.2Hz), 3.30(1H, d, J=16.8Hz), 3.84(1H, d, J=16.8Hz), 4.32(3H, s), 4.32-4.45(1H, m), 5.19(1H, d, J=5.0Hz), 5.75(1H, dd, J=5.0, 8.4Hz), 7.63(1H, s), 8.12(1H, d, J=6.68z), 8.16(2H, bs), 8.58(1H, d, J=6.8Hz), 9.61(1H, d, J=8.4Hz).

[0080] Example 39

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-ethoximinoacetamide]-3-(5-methylthieno[3,2-c]pyridinium-2-yl)thio-3-cefem-4-carboxylate

IR (KBr): 1765, 1660, 1610.

NMR (DMSO-d_6): 1.22(3H, t, J=7.0Hz), 3.23(1H, d, J=17.2Hz), 3.70(1H, d, J=17.2Hz), 4.15(1H, q, J=7.0Hz), 4.37(3H, s), 5.11(1H, d, J=4.8Hz), 5.69(1H, dd, J=4.8, 8.4Hz), 7.83(1H, s), 8.13(2H, bs), 8.63(2H, s), 9.40(1H, s), 9.58(1H, d, J=8.4Hz).

Example 40

In the same manner as Example 1, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-ethoximinoacetamide]-3-[(E)-2-(5-methylthiazolo[3,2-c]pyridinium-2-yl)thioethenyl]-3-cefem-4-carboxylate

IR (KBr): 1760, 1675, 1600.

NMR (DMSO-d_6): 1.27(3H, t, J=7.0Hz), 3.49(1H, d, J=17.0Hz), 3.61(1H, d, J=17.0Hz), 4.18(2H, q, J=7.0Hz), 4.18(2H, q, J=7.0Hz), 4.39(3H, s), 5.08(1H, d, J=4.8Hz), 5.65(1H, dd, J=4.8, 8.8Hz), 6.52(1H, d, J=15.4Hz), 7.49(1H, d, J=15.4Hz), 7.81(1H, s), 8.16(2H, bs), 8.64(2H, s), 9.40(1H, s), 9.54(1H, d, J=8.8Hz).

[0081] Example 41

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoximinoacetamide]-3-[5-methyl-4-(1-methylpyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate

IR (KBr): 1770, 1680, 1640, 1610.

NMR (DMSO-d_6): 2.71(3H, s), 3.41(1H, d, J=16.8Hz), 3.85(1H, d, J=16.8Hz), 4.33(3H, s), 5.16(1H, d, J=5.2Hz), 5.73(1H, dd, J=5.2, 8.2Hz), 5.79(2H, d, J=55.2Hz), 8.23(2H, s), 8.32(2H, d, J=6.8Hz), 8.94(2H, d, J=6.8Hz), 9.84(1H, d, J=8.2Hz).

Example 42

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-ethoximinoacetamide]-3-[5-methyl-4-(1-methylpyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate

IR (KBr): 1770, 1665, 1640, 1610.

NMR (DMSO-d_6): 1.25(3H, t, J=7.0Hz), 2.70(3H, s), 3.42(1H, d, J=17.0Hz), 3.84(1H, d, J=17.0Hz), 4.17(2H, q, J=7.0Hz), 4.33(3H, s), 5.15(1H, d, J=4.8Hz), 5.72(1H, dd, J=4.8, 8.4Hz), 8.15(2H, s), 8.31(2H, d, J=6.6Hz), 8.94(2H, d, J=6.6Hz), 9.62(1H, d, J=8.4Hz).

[0082] Example 43

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-isopropoximinoacetamide]-3-[5-methyl-4-(1-methylpyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate

IR (KBr): 1770, 1670, 1640, 1610.

NMR (DMSO-d_6): 1.25(6H, m), 2.74(3H, s), 3.43(1H, d, J=16.6Hz), 3.85(1H, d, J=16.6Hz), 4.39(1H, m), 5.16(1H, d, J=5.2Hz), 5.72(1H, dd, J=5.2, 9.2Hz), 8.15(2H, s), 8.33(2H, d, J=7.2Hz), 8.95(2H, d, J=7.2Hz), 9.58(1H, d, J=9.2Hz).

Example 44

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoximinoacetamide]-3-[5-methyl-4-(1-carbamoylmethylpyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate

IR (KBr): 1770, 1690, 1640, 1610.

NMR (DMSO-d_6): 3.53(1H, d, J=16.8Hz), 3.91(1H, d, J=16.8Hz), 5.21(1H, d, J=5.2Hz), 5.37(2H, s), 5.77(1H, dd, J=5.2, 8.2Hz), 5.81(2H, d, J=55.2Hz), 7.72(1H, s), 8.25(3H, bs), 8.48(2H,d, J=6.6Hz), 8.91(2H, s), 8.92(2H, d, J=6.6Hz), 9.88(1H, d, J=8.2Hz).

[0083] Example 45

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-ethoximinoacetamide]-3-[5-methyl-4-(1-carbamoylmethylpyridinium-4-yl)thiazol-2-yl]thio-3-cefem-4-carboxylate

IR (KBr): 1770, 1690, 1640.

NMR (DMSO-d_6): 1.25(3H, t, J=7.4Hz), 3.40(1H, d, J=17.2Hz), 3.90(1H, d, J=17.2Hz), 4.17(2H, q, J=7.4Hz), 5.19(1H, d, J=5.2Hz), 5.36(2H, s), 5.47(1H, dd, J=5.2, 8.8Hz), 7.70(1H, s), 8.15(3H,bs), 8.48(2H, d, J=7.0Hz), 8.91(2H, s), 8.92(2H, d, J=7.0Hz), 9.63(1H,d, J=8.8Hz).

Example 46

In the same manner as Example 11, the following compound was produced.

7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(Z)-fluoromethoximinoacetamide]-3-[4-(1-methylpyridinium-4-yl) thiophene-2-yl]thio-3-cefem-4-carboxylate

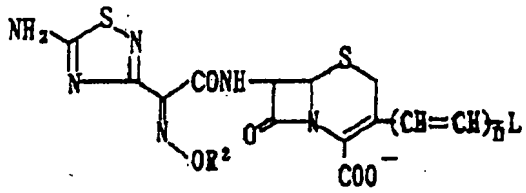
IR (KBr): 1760, 1670, 1635, 1605.

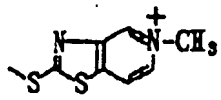
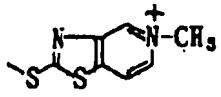
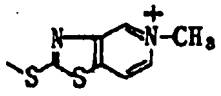
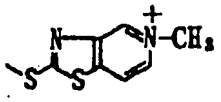
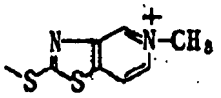
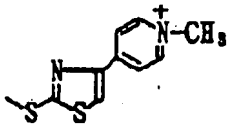
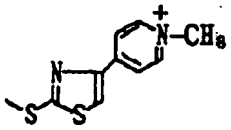
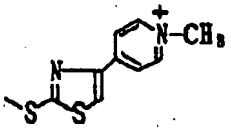
NMR (DMSO-d_6): 3.19(1H, d, J=16.8Hz), 3.54(1H, d, J=16.8Hz), 4.29(3H, s), 5.02(1H, d, J=4.8Hz), 5.62(1H, dd, J=4.8, 8.4Hz), 5.76(2H, d, J=55.8Hz), 8.04(1H, d, J=1.2Hz), 8.25(2H, bs), 8.43(2H, d, J=6.6Hz), 8.78(1H, d, J=1.2Hz), 8.95(2H, d, J=6.6Hz), 9.74(1H, d, J=8.4Hz).

The structural formulas of the compounds of Examples are shown below.

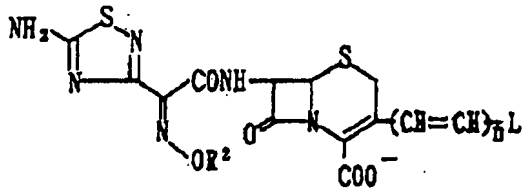
[0084]

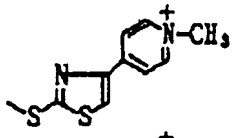
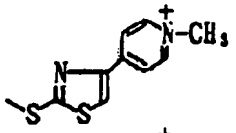
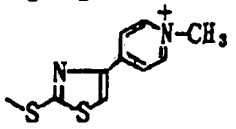
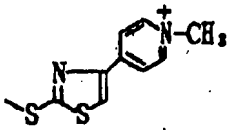
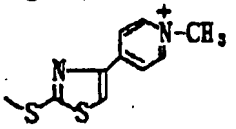
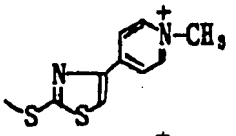
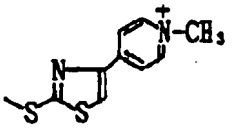
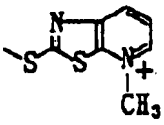
[Table 1]



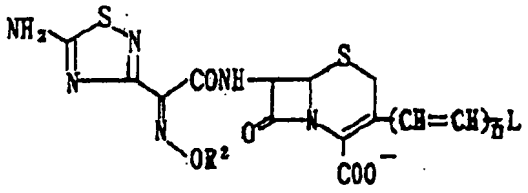
Example No.	R^2	n	L
1	CH_3	1	
2	CH_2F	1	
3	C_2H_5	1	
4	$CH(CH_3)_2$	1	
5		1	
6	Me	1	
7	CH_2F	1	
8	C_2H_5	1	

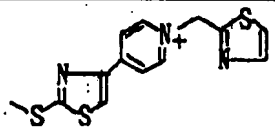
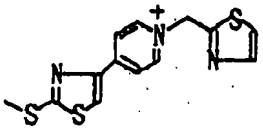
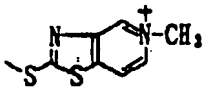
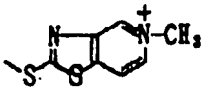
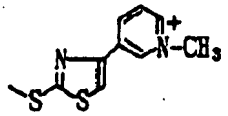
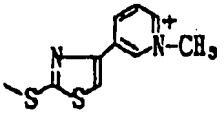
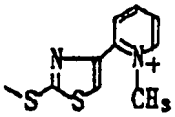
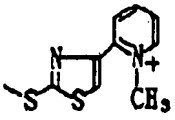
[0085]
[Table 2]



Example No.	R^2	n	L
9	$CH(CH_3)_2$	1	
10		1	
11	$CH(CH_3)_2$	0	
12	CH_2F	0	
13	C_2H_5	0	
14		0	
15	CH_3	0	
16	CH_2	1	

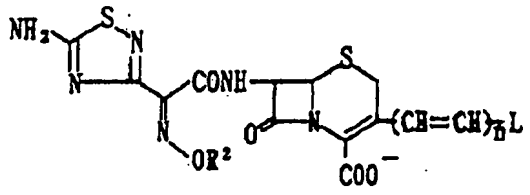
[0086]
[Table 3]

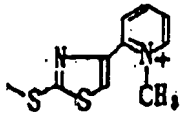
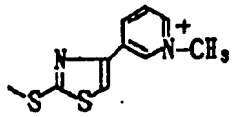
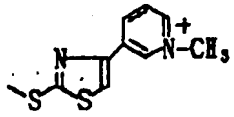
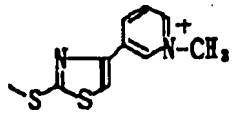
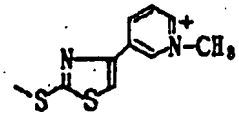
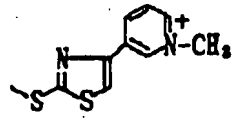
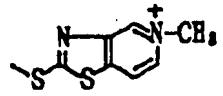
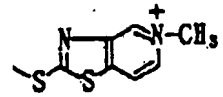


Example No.	R^2	n	L
17	CH_3	0	
18	CH_2F	0	
19	CH_3	0	
20	CH_2F	0	
21	CH_3	0	
22	CH_2F	0	
23	CH_3	0	
24	CH_2F	0	

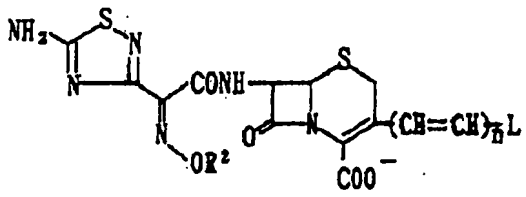
[0087]

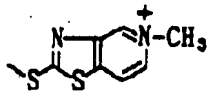
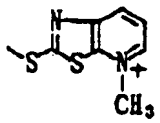
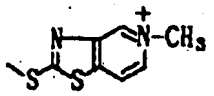
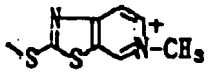
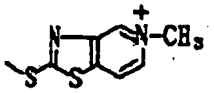
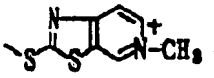
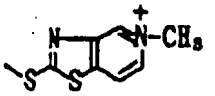
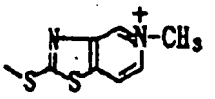
[Table 4]



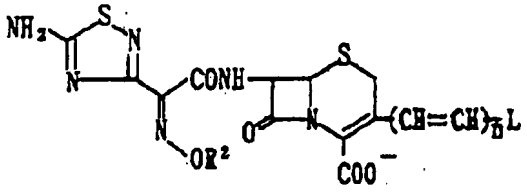
Example No.	R^2	n	L
25	$CH(CH_3)_2$	0	
26	CH_3	0	
27	CH_2F	0	
28	$CH(CH_3)_2$	0	
29	$CH(CH_3)_2$	0	
30	C_2H_5	0	
31	CH_3	0	
32	CH_2F	0	

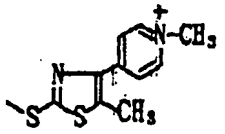
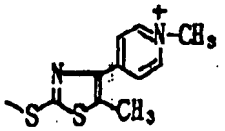
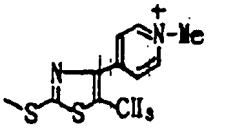
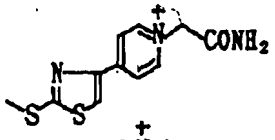
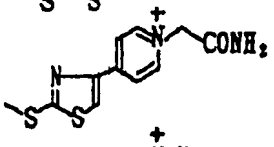
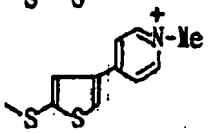
[0088]
[Table 5]



Example No.	R^2	n	L
33	CH_2F	1	
34	CH_2F	1	
35	$CH(CH_3)_2$	1	
36	CH_2F	0	
37	$CH(CH_3)_2$	1	
38	$CH(CH_3)_2$	0	
39	C_2H_5	0	
40	C_2H_5	1	

[0089]
[Table 6]



Example No.	R^2	n	L
41	CH_2F	0	
42	C_2H_5	0	
43	$CH(CH_3)_2$	0	
44	CH_2F	0	
45	C_2H_5	0	
46	CH_2F	0	

[0090] Test Example 1

The minimal inhibitory concentration (MIC) of the test compound was determined using the agar dilution method. Specifically, 1.0 ml of a serially diluted aqueous solution of the test compound was poured in a petri dish, after which 9.0 ml of Trypticase soy agar was poured and mixed. Over the mixed agar plate, a suspension of each test strain (about 10^6 CFU/ml) was applied. After overnight incubation at 37°C, the minimal concentration of the test compound that completely inhibited the growth of the test strain was taken as MIC.

Test strains:

(1) *Staphylococcus aureus* N133 (MRSA)

(2) *Staphylococcus aureus* OFU4 (MRSA)

Results:

[0091]

[Table 7]

Example No.	MIC (μg/ml)	
	Test strain (1)	Test strain (2)
2	1.56	1.56
3	1.56	1.56
4	1.56	3.13
5	0.78	1.56
10	1.56	1.56
11	1.56	1.56
12	1.56	3.13
13	1.56	3.13
14	1.56	1.56
18	1.56	1.56
21	3.13	1.56
22	1.56	1.56
25	3.13	1.56
28	3.13	1.56
29	1.56	1.56
30	1.56	1.56
32	1.56	1.56
33	1.56	1.56
35	0.78	0.78
38	1.56	1.56
39	1.56	1.56
40	1.56	1.56
41	1.56	1.56
42	1.56	1.56
43	1.56	1.56
44	1.56	1.56
45	1.56	1.56

From these results, it is evident that the cefem compound [I] of the present invention or salt thereof or ester thereof exhibits excellent antibacterial action against clinically important pathogenic bacteria, especially MRSA.

[0092]

[Effect of the Invention]

Cefem compound [I] of the present invention, or an ester thereof or a salt thereof exhibits a broad spectrum of excellent antibacterial action against gram-negative bacteria, including the genus *Pseudomonas*, and gram-positive bacteria, including staphylococci and MRSA, and can provide an effective antibacterial agent for infectious diseases caused by these bacteria.